FISH CONSUMPTION AND DEMENTIA IN OLDER PEOPLE:
Impacts and Determinants

AISHAT TAIWO BAKRE

BSc (Hons), MPH, MSc
Faculty of Education, Health and Wellbeing
University of Wolverhampton
United Kingdom

A thesis submitted in partial fulfilment of the requirement of the University of Wolverhampton for the Degree of Doctor of Philosophy

January 2020

DECLARATION

I certify that this work or any part thereof has not previously been presented in any form to the University or to any other body whether for the purposes of assessment, publication or for any other purpose (unless otherwise indicated). Save for any express acknowledgments, references and/or bibliographies cited in the work, I confirm that the intellectual content of the work is the result of my own efforts and of no other person.

The right of Aishat Taiwo Bakre to be identified as the author of this work is asserted in accordance with ss.77 and 78 of the Copyright, Design and Patents Act 1988. At this date, the copyright is owned by the author.

…….. Aishat T. Bakre**…….**	...…31st January 2020…….
Signature	Date

DEDICATION

This thesis is dedicated to Almighty God for His infinite mercies and protection throughout this PhD journey.

ACKNOWLEDGEMENT

My greatest appreciation goes to Almighty God, who has given me sound health, strength and ability to complete this programme despite all odds.

I would like to express my sincere appreciation and gratitude to my amiable supervisors Professor Rouling Chen and Dr Angela Clifford for their support, attention, understanding and role throughout the course of this research programme; their series of advice, suggestions, encouragement and dedication have gone a long way in strengthening me during this programme and have contributed immensely to achieving this great task. Also, I would like to thank Dr Martin Partridge for his support and significant contribution towards the completion of the qualitative part of this research, Dr Yuyou Yao for the Chinese dataset management, and Dr James J Tang for his guidance on data analysis.

I also express my gratitude to my parents, Alhaji & Alhaja O.K. Bakre, my twin sister and her husband Dr & Dr Mrs Akodu for their moral, financial and unwavering support throughout this research programme.

My deepest thanks also go to the study participants for contributing and sharing their experiences. The completion of this thesis would not have been possible without their contributions.

My appreciation goes to the academic staff members of the Centre for Health and Social Care Improvement (CHSCI) and the non-academic staff members of the Faculty of Education Health and Wellbeing (FEHW), their contributions are well respected and valued.

Finally, I would like to acknowledge the role played by my friends and colleagues toward the success of this programme. Their concerns and encouragement are all highly appreciated and may God Almighty reward you abundantly.

Funding: The presentations of the parts of this study in the 4th International Conference on Epidemiology and Public Health, 3rd-5th October 2016, London, England, and in the Alzheimer's Research UK Conference, 14th-15th March 2017, Aberdeen, Scotland were supported with the QR travel grants from the Faculty of Education, Health and Wellbeing, University of Wolverhampton.

ABSTRACT

Background: Dementia is one of the world's biggest health problems and is a major public health challenge that is becoming more common as the aged population grows. There is no known cure for dementia, and thus more efforts have been made to investigate its risk or protective factors for prevention. Previous studies suggested that increased consumption of fish reduces the risk of cardiovascular diseases. However, it is unclear whether the consumption of fish was associated with the risk of dementia and outcomes of people with dementia. Also, few studies have specifically examined factors influencing the consumption of fish in older people, despite the world population aging. The purpose of this research project was to conduct a systematic literature review and examine the determinants and impacts of fish consumption on the incidence and mortality of dementia in older people using a convergent parallel database mixed methodological approach.

Methods: This study employed a systematic literature review and a mixed method of quantitative and qualitative approaches that is based on a large cohort study dataset from China and two focus group discussions from the United Kingdom. In 2007-2009, 6071 participants aged ≥60 years were randomly selected from urban and rural communities in five-provinces, China. Using a standard interview method, participants' socio-economic status, disease risk factors and fish consumption over the past two years were documented at baseline and this was followed up until 2012. The data of the cohort were analysed in multivariate adjusted logistic regression and Cox proportional hazards regression models. In 2018, the focus group discussions that consisted of 12 older adults were conducted in the UK, and the qualitative data was analysed using thematic analysis.

Results: The findings of these studies demonstrated that increased consumption of fish was associated with reduced risk of dementia and all-cause mortality among older people. The study also examined and found that large socioeconomic inequalities, and certain lifestyle, psychosocial factors and health-related conditions are significant determinants of fish consumption. The qualitative study further revealed that participants consume fish for its taste, flavour, the desire for variety of food and the nutritional and health benefit including reducing the risk of dementia and other health outcomes. Although cost, bony/scaly fish, smell and availability/accessibility of fish were highlighted as the major barriers of fish consumption.

Conclusions: This research has provided evidence for preventing dementia and reducing all-cause mortality through adequate fish consumption. The findings of the study should be extended to improve public health policy, and this could form the basis for further research.

MY PUBLICATIONS AND PRESENTATIONS DURING PHD STUDY

Journal Papers

1. **Bakre, A.T.,** Chen, R., Khutan, R., Wei, L., Smith, T., Qin, G., Danat, I.M., Zhou, W., Schofield, P., Clifford, A., and Wang, J. (2018) Association between fish consumption and risk of dementia: a new study from China and a systematic literature review and meta-analysis. *Public Health Nutrition Journal*, 21(10), pp.1921-1932.
2. **Bakre, A.T.,** Song, Y., Clifford, A., Chen, A., Smith, T., Wan, Y., Devlin L., Jie Tang, J., Zhou, W., Danat, I.M., Hu, Z., Chen, R. (2018) Determinants of fish consumption in older people: a community-based cohort study. *Journal of Aging Research & Clinical Practice*, 7, pp.163-175.
3. Danat, I.M., Clifford, A., Partridge, M., Zhou, W., **Bakre, A.T.,** Chen, A., McFeeters, D., Smith, T., Wan, Y., Copeland, J., and Anstey, K.J., Chen, R. (2019) Impacts of Overweight and Obesity in Older Age on the Risk of Dementia: A Systematic Literature Review and a Meta-Analysis. *Journal of Alzheimer's Disease*, 70(1) pp. 87-99.
4. Nadim, R., Tang, J., Dilmohamed, A., Yuan, S., Wu, C., **Bakre, A.T.,** Partridge, M., Ni, J., Copeland, J.R., Anstey, K.J., and Chen, R. (2020) Influence of periodontal disease on risk of dementia: a systematic literature review and a meta-analysis. *European Journal of Epidemiology*, pp.1-13.

Papers Presented at International and National Conference

5. **Bakre, A.T.,** Tang., J., Clifford, A., Chen, R. (13th-14th June 2019) Impact of fish consumption on all-cause mortality in older people with and without dementia: a community-based cohort study. Oral Presentation at the 9th European Epidemiology and Public Health Conference, Helsinki, Finland
6. **Bakre, A.T.,** Clifford, A., Chen, R. (20th-23rd August 2018) Determinants of fish consumption in older adults: a community-based cohort study. Oral Presentation at the International Conference of Global Health and Epidemiology, Telford, England, UK
7. **Bakre, A.T.,** Clifford, A., Chen, R. (13th-15th March 2017) Impact of fish consumption on the risk of Alzheimer's disease: a systematic literature review and a meta-analysis. Poster Presentation at the Alzheimer's Research UK (ARUK) conference, Aberdeen, UK
8. **Bakre, A.T.,** Chen, R., Clifford, A. (03rd-05th October 2016) Association between fish consumption and risk of dementia: a systematic worldwide literature review and a new study from China. Oral Presentation at the 4th International Conference on Epidemiology and Public Health, London, UK

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AD: Alzheimer’s Disease

ADL: Activity of Daily Living

AGECAT: Automated Geriatric Examination for Computer Assisted Taxonomy

ALA: Alpha Linoleic acid

APOE-e4: Apolipoprotein E

ARA: Arachidonic Acid

BMI: Body Mass Index

CERAD: Consortium to Establish a Registry for Alzheimer’s Disease

CHAP: Chicago Health and Aging

CHD: Coronary Heart Disease

CI: Confidence Interval

CINAHL: Cumulative Index to Nursing and Allied Health Literature

COGSCORE: CSI-D Cognitive test Score

COPD: Chronic Obstructive Pulmonary Disease

CSI-D: Community Screening Instrument for Dementia

CVD: Cardiovascular Disease

DHA: Docosahexaenoic acid

DSM: Diagnostic and Statistical Manual of Mental Disorders

ETS: Environmental Tobacco Smoke

EPA Eicosapentaenoic acid

FAO: Food and Agricultural Organisation

FFQ-Food-Frequency Questionnaire

GMS: Geriatric Mental State

HBM: Health Belief Model

HIC: High Income Country

HR: Hazard Ratios

IQCoDE-Informant Questionnaire for Cognitive Decline in the Elderly

IQ: Intelligence Quotient

LDC: Least Developed Countries

LIFDCs: Low-Income Food-Deficit Countries

LMIC: Low- and Middle-Income Countries

MCI: Mild Cognitive Impairment

MD: Mixed Dementia

MI: Myocardial Infarction

MMSE: Mini-Mental Status Examination

MRI: Magnetic Resonance Imaging

NINCDS-National Institute of Neurological and Communicative Diseases and Stroke-

ADRDA- AD and Related Disorders Association

OR: Odds Ratio

PD: Parkinson Disease

PEO: Population, Exposure and Outcome Framework

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PR: Prevalence Ratio

PUFAs: Polyunsaturated fatty acids

RELSCORE: CSI-D informant interview

RCT: Randomized Control Trial

RR: Relative Risk

TICS: Telephone Interview for Cognitive Status

TPB: Theory of Planned Behaviour

TRA: Theory of Reasoned Action

T2D: Type 2 Diabetes

TG: Triglycerides

VD: Vascular Dementia

WC: Waist Circumference

WHO: World Health Organisation

WPIS: Wolverhampton Profile Information and Statistics

CHAPTER ONE: INTRODUCTION

1.0 Introduction

This chapter provides an overview and background information for this research. It includes fish and types of fish, its nutritional components, and the global overview of fish consumption. This chapter also presents a brief outline of the thesis structure.

1.1 Overview of the Research

There is a tendency that life expectancy among the aged population will increase, since mortality among them is reducing (Prince *et al.,* 2015), thereby increasing the prevalence of chronic non-communicable diseases including cardiovascular diseases (CVD) and neurodegenerative disorders such as dementia. Therefore, urgent and effective strategies need to be implemented to reduce or prevent the burden of these diseases through risk reduction and lifestyle modification, which include the consumption of a healthy and balanced diet.

There is increasing interest and expectation in the role nutrition plays in the prevention of chronic non-communicable diseases. Appropriate nutrition is a vital modifiable lifestyle factor that benefits the promotion of good health among the populace (Darnton *et al.,* 2004; Lee *et al.,* 2010). In the past decades, there has been growing interest in the consumption of fish, a source of long-chain omega-3 polyunsaturated fatty acids (PUFAs), with evidence from population-based studies suggesting its protective effect on some chronic non-communicable diseases. This could be due to their anti-inflammatory (Calder, 2013), anti-atherosclerotic, antithrombotic (Chapkin *et al.,* 2007), antiarrhythmic and antiatherogenic properties (Mori, 2017). Additionally, fish is a high-quality animal protein with other essential nutrients including vitamins and minerals that are beneficial to health (Lund, 2013). Fish and its constituents (omega-3 PUFAs) play a crucial role in the development of the brain and the maintenance of brain lipids (Innis, 2007; Cunnane *et al.,* 2009), and could therefore possibly influence the cognitive well-being of the aged population.

It is generally acknowledged that human cognitive capabilities deteriorate as age increases (Wittchen *et al.,* 2011). This varies in magnitude among different people, where some express no or slight decline in cognitive function at old age while others show a major decline which could later deteriorate into dementia that affects the quality of life of the individual (Schaie, 2005; Deary *et al.,* 2010). Although aging is the greatest risk factor ascribed to dementia (Qiu, Kivipelto and von Strauss, 2009) and the biological processes of aging may have tremendous impact on the pathogenesis of its development (Qiu, Kivipelto and von Strauss, 2009), dementia is not necessarily a normal part of aging.

Dementia is one of the world's biggest health problems and is a major public health challenge that is becoming more common as the aged population grows. Dementia is characterised by memory loss and impairment to other cognitive parts of the brain (Ogawa, 2014). The causes of dementia are unclear. Its incidence continues to increase worldwide and especially in low- and middle-income countries, including China, where availability of social services, care and support are deficient (Prince *et al.,* 2015; WHO, 2015). There is no known cure for dementia, and thus more efforts have been made to investigate its risk or protective factors for prevention.

As there is further increase in the inevitability of developing a decline in cognitive function among some older people due to build-up of molecular damage to nerve cells that occurs throughout the life course (Denny, 2008; Jack *et al.,* 2010; Jack *et al.,* 2013), it is therefore paramount to better understand the modifiable lifestyle factors that can prevent or delay the age associated pathological changes in cognitive behaviour. Human nutrition is on the top list (Prince *et al.,* 2014). There is a need to tailor research towards a dietary factor that could possibly help to reduce the risk or delay the onset of this cognitive disorder (Qiu, Kivipelto and von Strauss, 2009). This is important for prolonging independent living and maintaining the cognitive health of the population as they advance in age. This could markedly help to lessen the burden of dementia by reducing the number of dementia patients requiring a high level of care and support.

Previous studies suggested that increased consumption of fish reduces the risks of cardiovascular diseases (e.g. coronary heart disease (CHD) (Zheng *et al.*, 2012), stroke (Xun *et al.*, 2011), respiratory disease (Yang *et al.*, 2013), certain cancers (Wu *et al.*, 2012; Dai *et al.*, 2017), type 2 diabetes (Zhang *et al.*, 2013), depression (Li *et al.*, 2016) and all-cause mortality (Zhao *et al.*, 2015). But its impacts on the risk of dementia and outcomes of people with dementia are unclear. Few studies have been carried out to examine the association between fish consumption and the risk of dementia, and their findings are inconsistent. These studies are predominantly from the HIC countries, and data from low- and middle-income countries (LMIC) is lacking. In addition, few studies have examined the factors influencing the consumption of fish in older people. Therefore, the focus of this thesis is to examine the determinants and impacts of fish consumption on the incidence and prognosis of dementia in older people using convergent parallel databases mixed methodological approach.

The following sections cover the thesis outline and background including fish and types of fish, its nutritional components, and the global overview of fish consumption.

1.2 Outline of the Thesis

This thesis addresses the global health impacts of fish consumption on the incidence and prognosis of dementia using a mixed method approach that is based on an existing secondary cohort dataset (quantitative study) in China and a qualitative study in the United Kingdom. This thesis presents six original data studies and systematic literatures and meta-analysis findings. These include one cross-sectional study and three cohort studies in China, a qualitative study based on 2 focus group discussions in the UK and a new comprehensive systematic worldwide literature review and a meta-analysis.

The strategy needed to lessen the risk of dementia should focus on research that examines some modifiable lifestyle factors such as diet and the determinants that can affect the proper consumption of the diet. This present doctoral research helps to explain one of these dietary factors. It focuses on fish consumption and its association with dementia risk and outcomes and examines the determinants of fish consumption in older people. The thesis is divided into six distinct studies with an overarching theme that reflect fish consumption as a modifiable lifestyle factor in reducing the risk of dementia, and the determinants that affect its inadequate consumption. The first Chapter sets the context. This chapter provides an overview of the research topic, the background including fish and types of fish, its nutritional components and the global overview of fish consumption. The second Chapter focuses on the literature review. This chapter presents the health effects of fish consumption in relation to cardiovascular disease (CVD) including (stroke and coronary heart disease (CHD)), respiratory disease (COPD and asthma), certain cancer types, diabetes mellitus, mental health (depression and other psychiatric illness) and all-cause mortality. This is followed by dementia epidemiology and the association of fish consumption with incidence and prognosis of dementia as well as the factors influencing the consumption of fish with detailed explanation of the conceptual framework employed in this thesis. The third Chapter describes the methodology adopted throughout the thesis. It highlights the rationale for the chosen methods including data collection, analysis and ethical considerations including the trustworthiness of the study. The fourth Chapter reviews the impact of fish consumption on the risk of dementia using a systematic literature review approach. The fifth Chapter investigates the determinants of fish consumption in older people via a community-based cohort study. The sixth Chapter examines the association of incident dementia with fish consumption in older age through exploring a new cross-sectional study from China and a meta-analysis. The seventh Chapter examines the association of incident dementia with fish consumption in older age by exploring a new cohort study from China and an updated meta-analysis of cohort studies. The eighth Chapter explores the impact of fish consumption on all-cause mortality through a community-based cohort study in older people with and without dementia. The ninth Chapter presents the qualitative findings of this thesis that involve the use of two focus group discussions to explore the determinants and impacts of fish consumption on dementia and other health outcomes. The tenth Chapter presents the overall discussion by presenting the summary of key findings and the integration of all the findings of previous chapters. It also presents the strengths, limitations and suggestions for future research, the implications of findings and recommendations and lastly the contribution to knowledge and conclusions of the thesis. This is followed by the references and appendices.

1.3 Background

1.3.1 Fish and Types of Fish

Fish are limbless cold-blooded aquatic animals that possess gills and fins (Gartside and Kirkegaard, 2010). The definition of fish for the purpose of this thesis will encompass both wild and farmed aquatic animals with gills and fins from both marine and freshwater source in fresh, frozen and processed forms (Gartside and Kirkegaard, 2010; Weichselbaum *et al.,* 2013). Fishes consist of scale/fin fishes, bony (e.g. catfish and tuna), and cartilaginous fishes (e.g. sharks and rays) (Gartside and Kirkegaard, 2010). Globally, fish serve as a source of food for human consumption (Tidwell and Allan, 2001). This was achieved through the act of fishing, a practice of fish catching. The catching of fish, an important component of the human diet started 50,000 years ago during the Upper Paleolithic era (Sahrhage and Lundbeck, 1992). During this period, fishing vessels were used to cross the ocean in search of fish to catch. This fishing practice started since the 16th century with further advancement in the 19th century, when larger fishing vessels were utilised, or some fish processing were carried out on board (Sahrhage and Lundbeck, 1992; Gartside and Kirkegaard, 2010). Fish can be caught through several fishing techniques, which include hand gathering, spearing, netting, angling, and trapping (Sahrhage and Lundbeck, 1992).

1.3.1.1 Types of Fish

Globally, there are over 30,000 various types of fish with yearly discovery of new species (Martin, 2017). Fish are classified into both fatty and lean fish (Calder, 2004). The fatty fish are rich sources of omega-3 PUFAs (EPA and DHA) that store fat as triglycerides (TGs) in their flesh (Calder, 2004; Gazi *et al.,* 2006). They include salmon, sardines, herring (e.g. bloater, kipper and hilsa), sprats, mackerel, trout, tuna, bass, bluefish, anchovies, sablefish, and pilchards (Sidhu, 2003;

Huang *et al.,* 2005; Domingo *et al.,* 2007; Chang *et al.,* 2009; Fotuhi, Mohassel, Yaffe, 2009; Mori, 2017). The lean fish with low fat content and lower level of omega 3 PUFAs stored as TGs in the liver include white fish such as cod, haddock, plaice, pollack, coley, flounder, hake, sea bass, sole, turbot and halibut (Huang *et al.*, 2005; Lund, 2013).

1.3.2 Nutritional Components

Fish is a multi-component nutritional source of high-quality animal protein that plays a significant role in world food security and human nutrition (Sidhu, 2003; FAO, 2018). Fish is an important source of essential nutrients, including vitamins, minerals and amino acids (Sidhu, 2003; Kawarazuka, 2010; Lund, 2013), which provides an adult with the required protein of approximately 50-60% from a daily serving of 150g (FAO, 2018). Fish consumption has contributed immensely to the prevention of chronic diseases over the years (Xun *et al.,* 2011; Zheng *et al.,* 2012), because of its long chain omega-3 polyunsaturated fatty acids (PUFAs) constituent. Long chain omega-3 PUFAs comprise docosahexaenoic acid (DHA, C22:6) and eicosapentaenoic acid (EPA, C20:5), and they are collectively called the fish essential fatty acids (EFA) (Connor, 2000; Uauy and Dangour, 2006; Connor, 2007; Innis, 2007; Dangour *et al.*, 2009, Lund, 2013; Wu *et al.*, 2015). These fish EFA constitute up to one third of fat in the muscle of fish and are important constituents for proper brain and retina functioning as well as neurocognitive development (Connor, 2000; Salem *et al.,* 2001; Wu *et al.,* 2015), since the nervous system is largely made of approximately 50-60% lipid, of which PUFAs account for 35% (Wainwright, 2002; Haag, 2003; Chang *et al.,* 2009). Docosahexaenoic acid (DHA), an important omega-3 PUFA, is a major component of the phospholipids of nerve cell membranes in the brain with vascular, oxidative and anti-inflammatory properties (Connor, 2000; Yehuda *et al.,* 2002; Bloomer *et al.,* 2009), while EPA is majorly concentrated in the liver and human muscle (Arterburn *et al.,* 2006). DHA is primarily found in oily cold-water fish and some other seafood, because they consume algae and plankton that are their main source (Chang *et al.*, 2009; Lopez *et al.*, 2011). DHA and EPA cannot be directly synthesised in the body unless the synthesis is initiated by a precursor called alpha-linolenic acid (ALA) [18:2(n-3)], which is their recognised functional role, but the rate of synthesis is quite low (Singh, 2005; Das, 2006; Fotuhi, Mohassel, Yaffe, 2009). This ALA is a short chain omega-3 PUFAs that is present in minute quantity in plants including avocados, soybeans, almonds, walnuts, pumpkin and vegetable oils such as flaxseed, soy, peanut, canola, and linseed (Chang *et al.*, 2009; Cole and Frautschy, 2010; Mori, 2017).

1.3.3 Global Overview of Fish Consumption

Fish production has significantly increased over the years with an average annual fish supply rate of 3.2%, thereby improving the global rate of consumption (FAO, 2018). Globally, it was estimated that the per capita fish consumption growth rose from 9.0kg in 1961 to 20.2kg in 2015, with a preliminary estimate of 20.3kg and 20.5 kg for 2016 and 2017 respectively, reflecting an average annual increment of at least 1.5% (FAO, 2018). This upsurge in the rate of fish consumption has been achieved through an increase in the rate of production and some other factors including urbanisation, increasing income, effective distribution channels, increasing demand, population growth and waste reduction (FAO, 2018). In 2015, the quantity of fish consumed worldwide was almost 17% of the total animal protein consumed globally and 7% of all sources of proteins, thus providing approximately 3.2 billion people worldwide with approximately 20% of an average per capita animal protein intake (FAO, 2016; FAO, 2018). Fish and its products provide approximately 34 calories per capita per day to the world population, but this estimation could exceed 130 calories in regions that depend solely on fish protein as their major source of animal protein in the absence of other protein sources (FAO, 2018). These include the Republic of Korea, Iceland, and several small Island States (FAO, 2018).

There is low consumption rate of fish protein among people in the low- and middle-income countries (LMIC) (FAO, 2018). The percentage rate of fish consumption in 2015 was approximately 26% of the animal protein intake in the least developed countries (LDCs), 19% in some other developing countries and approximately 16% in the low-income food-deficit countries (LIFDCs). This increment has occurred over the years, but recently appears stable due to the increase in the intake of other sources of animal protein (FAO, 2018). Due to the influences of the cultural, economic and geographical factors, there is a significant variation in the average per capita fish consumption across and within countries (FAO, 2018). This varies between <1kg to >100kg across countries, while the within country consumption variation is typically higher in the coastal marine and inland water regions (FAO 2018). Despite the steady growth in the annual per capita fish consumption from 6.0kg in 1961 to 19.3kg in 2015 in the LMIC countries, the consumption rate is still significantly higher in HIC countries with 24.9 kg in the same year, even though the gap is gradually reducing (FAO, 2018).

In 1961, 47% of the world total food fish was consumed in Japan, Europe and the United States of America (USA), while in 2015; approximately 20% of total food fish was only consumed. Additionally, in 2015, greater than two-third of the global total food fish of 149 million tonnes was consumed in the Asian countries. This is equivalent to 106 million tonnes at 24kg per capita. In the same year, the lowest food fish consumption was experienced in Africa and the Oceania. This could be due to changes in the structure of the fishing sector and increasing rate of fish production in the Asian countries. It could also be due to the substantial gap in the economic advancement of the well-established global fish markets and the gradually evolving markets worldwide, especially in the Asian region (FAO, 2018). The advancement in the rate of fish consumption occurring in the Asian countries especially in the eastern part excluding Japan and south-eastern Asia was achieved through a combination of the following factors. These include urban population growth, dramatic increase in fish production especially from aquaculture, increasing incomes, and upsurge in the global fish trade.

In 2015, China was the highest fish consumer in the hierarchy of the countries in the global total fish consumption with a percentage of 38%, thus attaining approximately 41kg per capita fish consumption (FAO, 2018). This made the global annual per capita food fish consumption excluding China in 2015 to be approximately 15.5kg (FAO, 2018). The low fish consumption levels of 9.9kg per capita in the African countries persisted from 2015. This ranges from approximately 14 kg per capita in the west to 5kg per capita in the Eastern Africa with North Africa exhibiting a major progression from 2.8 to 13.9 kg per capita between the years 1961 to 2015, while some Sub-Saharan African countries still experienced a reduction in their per capita fish consumption level (FAO, 2018). This reduction in the fish consumption level was due to some certain interrelated factors. These include the population growing faster than the available food fish supply, lack of well-developed aquaculture sector, restricted fish production development, poor processing and storage facilities, poor marketing and distribution channels, and low level of income. The official statistics reported could be lower than the actual figures, due to under-reporting of the contribution of other fishing sectors including subsistence fish farming, small-scale fisheries and some across the border trade (FAO 2018). Nevertheless, some small island developing states (SIDS) top the highest in the per capita fish consumption with >50 kg especially in the Oceania, while the lowest level of slightly more than 2kg were experienced in the Central Asia and some other non-coastal countries (e.g. Afghanistan and Lesotho) (FAO, 2018).

However, because there is increasing interest in the prevention and modulation of chronic non-communicable diseases using a nutritional approach, fish consumption has attracted a lot of attention. As this is the focus of this thesis, its beneficial role and its health effects on the risk of some chronic diseases especially dementia will be elaborated in the following chapters through a review of existing literature.

CHAPTER TWO: HEALTH EFFECTS OF FISH CONSUMPTION AND EPIDEMIOLOGY OF DEMENTIA - *LITERATURE OVERVIEWS*

2.1 Overview of Chapter

This chapter presents the review of existing literature on the health effects of fish consumption in relation to cardiovascular diseases (CVD), respiratory disease, certain cancer types, diabetes mellitus, mental health, and all-cause mortality. This chapter begins by highlighting the various health benefits that can be derived from the consumption of fish. In addition, this chapter presents an overview of dementia epidemiology, the association of fish consumption with incidence and prognosis of dementia, and the factors influencing the consumption of fish. It also presents an overview of the conceptual frameworks used in this study. The chapter concludes with the rationale for this research and the aim and objectives of this research.

2.2 Introduction

Modifiable risk factors such as the consumption of fish are key modulators of several risk factors associated with chronic diseases (Connor, 2002; Lund, 2013). Fish consumption has been attributed to various health benefits (Lund, 2013). Evidence has shown the significant role that fish consumption plays in the prevention and treatment of several chronic diseases associated with ageing including cardiovascular diseases (CVD) (e.g. stroke and coronary heart disease (CHD)) and neurodegenerative disorder, thus promoting the health and wellbeing of the aged population. Fish and its constituents (omega-3 PUFA) play a crucial role in the development of the brain and the maintenance of brain lipids (Innis, 2007; Cunnane *et al.,* 2009). They are essential from conception through the birth and development of a child and certainly across the life course (Connor, 2000; Ruxton *et al.*, 2004; Innis, 2007; Gil and Gil, 2015). These fish constituents display anti-inflammatory (Calder, 2013), anti-atherosclerotic, antithrombotic (Von Schacky and Harris, 2007; Chapkin *et al.,* 2007), antiarrhythmic and antiatherogenic properties (Thorgilsson, Nunes and Gunnlaugsdóttir, 2010; Mori, 2017). They engage in the normal functioning and synthesis of brain neurotransmitters and immune system molecules (Chang *et al.,* 2009; Mischoulon and Freeman, 2013). They improve the endothelial function and blood flow to the brain (Tsukada *et al.,* 2000; Wang *et al.,* 2012). They modulate cellular metabolic functions and the expression of genes (Seo *et al.,* 2005; Cederholm *et al.,* 2013). This involves alterations of inflammatory processes as well as cellular membrane structure and functions (Seo *et al.,* 2005; Mischoulon and Freeman, 2013), thus resulting into alteration in nerve conduction, release and reuptake of neurotransmitter (Morris *et al.,* 2003). Omega-3 PUFA, especially DHA, display its neuroprotective role through several mechanisms. These include reducing arachidonic acid and its prostaglandin metabolites and increasing the transduction of downstream trophic signals (Cole *et al.,* 2009). DHA restricts the production and buildup of the β-amyloid peptide toxin and suppresses numerous transduction pathways signals (Combs *et al.,* 2000; Cole *et al.,* 2009). DHA also controls some of the kinases that phosphorylate the microtubule associated tau protein, hence improving the pathology of the neurofibrillary tangle, one of the hallmarks of AD pathogenesis. DHA reduces the signaling deficits of insulin and neurotrophic factor as well as increase the brain level of the neuroprotective brain-derived neurotrophic factor (Cole and Frautschy, 2010). DHA participates in cell signaling that is crucial and ideal for proper infants' neural development (Horrocks and Yeo, 1999). DHA is required in the synthesis of neurites: a nerve growth factor (Horrocks and Yeo, 1999), and for the proper development of the retina and visual cortex (Uauy and Dangour, 2006; Chang *et al.,* 2009). Deficiency of omega-3 PUFA causes impairment to the brain neurons, thus affecting the normal visual and neurological development (Innis, 2007; Barcelo-Colij and Murphy, 2009; Chang *et al.,* 2009).

However, since the consumption of fish is crucial for healthy ageing, there is obvious indication of its beneficial effect on the physical and mental wellbeing of humans, especially the cardiovascular and neurodegenerative disorders (Zhang *et al.,* 2016). Several studies have shown that fish consumption reduces the incidence of CVD (stroke) (Xun *et al.*, 2012) and coronary heart disease (CHD) (Zheng *et al.*, 2012), depression (Li *et al.*, 2016), respiratory disease (Yang *et al.*, 2013), type 2 diabetes (Zhang *et al.*, 2013), certain cancers (Wu *et al.*, 2012; Dai *et al.*, 2017) and all-cause mortality (Zhao *et al.*, 2013). But its association with the risk of dementia is unclear and the findings of previous studies are inconsistent. Also, the data from low- and middle-income countries (LMIC) is limited.

Therefore, the available studies on fish consumption and its association with each of these chronic diseases will be briefly summarised in the following sections with reference to the meta-analysis of existing human epidemiological studies and recent studies.

2.3 Fish Consumption and Cardiovascular Disease

Cardiovascular diseases including CHD and stroke are still the leading cause of morbidity and mortality worldwide (WHO, 2018). The beneficial effects of fish consumption and its omega-3 PUFAs constituent on the risk of CVD have been profoundly reported in various human epidemiological studies (Raatz *et al.*, 2013). A recent prospective cohort study including 20,969 Mediterranean participants aged ≥35 years old reported a 40% significant reduction in the risk of both composite CHD and stroke with hazard ratio (HR) (0.60, 95% CI 0.40-0.90) among participants that consumed fish ≥4 times/week when compared with those that consumed fish <2 times/week (Bonaccio *et al.*, 2017). While most studies showed an inverse association of fish consumption on the risk of CVD outcomes, others display non-inverse or no associations. A prospective cohort study of 39,876 female aged ≥45 years found no significant associations between the consumption of Tuna and dark fish, α-linolenic acid and marine omega-3 fatty acids and the risk of major cardiovascular disease and individual cardiovascular outcomes including myocardial infarction, ischemic and total stroke, and CVD death (Rhee *et al.,* 2017). Similar results were found in three previous meta-analyses of randomised control trials that found no association between the risk of CVD outcomes and omega-3 fatty acids supplementation a component of fish (Rizos *et al.,* 2012; Kotwal *et al.,* 2012; Kwak *et al.,* 2012). Rizos *et al.* (2012) meta-analysis of 20 studies including 68,680 participants found no significant associations of omega-3 fatty acids with the risk of some CVD outcomes including myocardial infarction (RR 0.89, 95% CI 0.76-1.04), stroke (RR 1.05, 95% CI 0.93-1.18), all-cause mortality (RR 0.96, 95% CI 0.91-1.02), cardiac death (RR 0.91, 95% CI 0.85-0.98) and sudden death (RR 0.87, 95% CI 0.75-1.01).

Overall, evidence from most cohort studies still supported the protective effect of fish consumption on CVD outcomes. The inconsistencies in the findings could be ascribed to several methodological differences among the relevant studies. These discrepancies in findings could be associated with the study designs, sample sizes, the length of exposure, dosage of fish consumption, types of fish consumed, adjustments for confounders, genetic susceptibility and reverse causation. In addition, the discrepancies in the findings could be due to the synergistic effect of the fish constituents including high-quality protein, vitamins and amino acids on CVD outcome, which could possibly be more effective on the association compared to the assessment involving only long-chain omega-3 PUFA (He, 2009).

The followings are the summaries of other related studies of the association between fish consumption and the risk of CVD (stroke and CHD) with reference to existing meta-analyses and recent studies.

2.3.1 Fish Consumption and Coronary Heart Disease

Coronary Heart Disease (CHD) that belongs to the large group of cardiovascular diseases is one of the leading causes of untimely deaths from non-communicable disease worldwide (WHO, 2011; WHO, 2014). Evidence from several epidemiological studies showed a protective effect of fish consumption on the risk of CHD, because of its richness in omega-3 PUFAs and its cardioprotective properties. Most of these studies have shown an inverse association between fish consumption and the risk of CHD, while others have found no inverse associations (Mann *et al.*, 1997; Oomen *et al.*, 2000; Mozaffarian *et al.*, 2003). These studies are summarised in the following three meta-analyses (He *et al.*, 2004a; Whelton *et al.*, 2004; Zheng *et al.*, 2012). In the meta-analysis by He *et al.* (2004a) including 13 cohorts from 11 studies, there was a reduction in the risk of CHD mortality among participants with a higher intake of fish with pooled (RR 0.89, 95% CI 0.79-1.01) for those that consumed fish at 1-3 times/month, 0.85 (0.76-0.96) for once/week, 0.77 (0.66-0.89) for 2-4 times/week, and 0.62 (0.46-0.82) for ≥5 times/week when compared to those who never/consumed fish <once/month. Similarly, a meta-analysis of 19 observational studies including 14 cohorts and 5 case-control studies by Whelton *et al.* (2004) revealed a 17% significant reduction in the risk of fatal CHD (RR 0.83, 0.76-0.90) and 14% for total CHD (RR 0.86, 0.81-0.92) among participants that consumed any amount of fish when compared to those with no or little fish consumption. Correspondingly, Zheng *et al.* (2012) meta-analysis of 17 cohort studies including 315,812 participants also reported a reduction in the risk of CHD mortality among participants with low fish consumption of 1 serving of fish/week (RR 0.84, 0.75-0.95), for moderate consumption of 2-4 servings/week (RR 0.79, 0.67-0.92) and (RR 0.83, 0.68-1.01) for high fish consumption of >5 servings/week when compared with the lowest fish consumption of <1 serving/month or 1–3 servings/month. The dose response relationship showed a 6% significant reduction in the risk of CHD mortality with every 15g/day increase in fish consumption level (RR 0.94, 0.90-0.98) (Zheng *et al.*, 2012). These findings were further supported by a recent cohort study (Bonaccio *et al.,* 2017). An Italian Moli-sani cohort study involving 20,969 Mediterranean participants aged ≥35 years with a median follow up period of 4.3 years found a 40% reduction in the risk of CHD with (HR 0.60, 0.38-0.94) among those participants that consumed fish ≥4times/week when compared to those with the lowest fish intake level of <2times/week (Bonaccio *et al.,* 2017).

Although most of the previously pooled studies showed an inverse association of fish consumption and the risk of CHD, some other individual studies demonstrated non-inverse associations or no associations. Hence, there are inconsistent results till date. This was revealed in a recent U.S veterans prospective cohort study of 508,699 participants aged ≥ 66 years old that were followed for a period of 2.9 years (Ward *et al.*, 2018). The authors found a non-consistent association with the risk of non-fatal CHD across all the fish consumption level of 1-3 servings/month, 1 serving/week, 2-4 servings/week, 5-6 servings/week, and >1 serving/day when compared with the lowest fish consumption level of <1 serving/month (Ward *et al.,* 2018). The heterogeneity in the findings could be explained by the possible existence of reverse causation, which arises when the occurrence of disease affects and changes the food consumption habits of individuals. It could also be due to the variation in the studies sample sizes, the length of follow-up, the type of fish assessed, the fish preparation method and the adjusted confounding variables in each of the studies. Even though all independent studies in the meta-analyses might have adjusted for known risk factors for CHD, there is the possibility of the presence of residual confounding factors.

In summary, it is obvious that most of the available cohort studies on the association of fish consumption with the risk of CHD show a beneficial risk reducing effect. Also, most of the pooled meta-analyses results suggested an inverse association of fish consumption with the risk of CHD, thereby indicating a convincing evidence of the protective effect of fish consumption on the risk of CHD.

2.3.2 Fish Consumption and Stroke

Stroke is one of the world leading causes of morbidity and mortality (WHO, 2018). Modifiable risk factors among which is diet have been associated with its risk reduction. Evidence from several epidemiological studies have shown a protective effect of fish consumption on the risk of stroke, which is ascribed to the presence of omega-3 PUFAs that has antiatherogenic, antiatherosclerosis, antithrombotic and anti-inflammatory effects (Rizos and Elisaf, 2013). An inverse association between fish consumption and the risk of stroke was found in most of these studies. These are summarised in four meta-analyses (He *et al.,* 2004b; Larsson *et al.,* 2011; Xun *et al.,* 2012; Zhao *et al.*, 2019). He *et al.* (2004b) meta-analysis of 9 cohorts from 8 independent studies showed a reduced risk of total stroke with pooled (RR 0.91, 95% CI 0.79-1.06) among individuals that consumed fish 1-3times/month, 0.87 (0.77-0.98) for those that consumed fish once a week, 0.82 (0.72-0.94) for 2-4 times/week and 0.69 (0.54-0.88) for ≥5 times/week when compared to individuals that consumed fish <once/month or never consumed fish. The respective pooled RR for stroke subtypes across all fish consumption levels from three of the included studies (Iso *et al.*, 2001; He *et al.,* 2002; Sauvaget *et al.,* 2003) were 0.69 (0.48-0.99), 0.68 (0.52-0.88), 0.66 (0.51-0.87), and 0.65 (0.46-0.93) for ischemic stroke and 1.47 (0.81-2.69), 1.21 (0.78-1.85), 0.89 (0.56-1.40) and 0.80 (0.44-1.47) for haemorrhagic stroke, thus showing inconsistent results among the stroke subtypes (He *et al.*, 2004).

In the dose-response meta-analysis of 15 prospective studies by Larsson *et al.* (2011), there was a 6% significant reduction in the risk of total stroke per increased intake of 3 portions of fish a week with relative risk (RR) 0.94 (0.89-0.99). In this meta-analysis, the stroke subtypes including 9 studies showed an inverse association with (RR 0.90, 0.84-0.97) for ischemic stroke and 0.90 (0.76-1.06) for haemorrhagic stroke per increased intake of 3 portions of fish a week. The sensitivity analysis showed estimated RRs ranging from 0.93 to 0.95, demonstrating that the pooled RR was not influenced by a single study. When the RRs for each fish consumption level in all the studies (i.e. highest and lowest level) were pooled together, it revealed a 12% reduced risk of stroke with (RR 0.88, 0.81-0.96). Similarly, Xun *et al.* (2012) meta-analysis of 19 cohorts from 16 studies showed a reduced risk of total stroke among participants that consumed fish at levels of 1–3/month, 1/week, 2–4/week, and ≥5/week with (HR 0.97, 0.87-1.08), 0.86 (0.80-0.93), 0.91 (0.85–0.98) and 0.87 (0.79-0.96) respectively when compared with those who never consumed fish or ate fish <1/month. The inverse associations were obvious with incidence of ischemic stroke but were weakened with haemorrhagic stroke (Xun *et al.*, 2012). This could be due to the different etiopathogenesis of these two stroke subtypes, where the antiplatelet protective effect of omega-3 PUFA on ischaemic stroke may be a risk factor for the development of haemorrhagic stroke (He, 2009). In a more recent meta-analysis of 33 prospective cohort studies from 31 published papers, a 10% significant reduction in the risk of stroke was found when the highest fish consumption level was compared with the lowest fish consumption level (HR 0.90, 0.85-0.96) (Zhao *et al.*, 2019). A linear dose response relationship of 2%-12% reduction in the risk of stroke was found with increased fish consumption of 100-700g a week. In contrast to He *et al*. (2004) meta-analysis of 9 cohort studies and Xun *et al.* (2012) meta-analysis of 19 cohort studies that found a weakened association of fish consumption with haemorrhagic stroke, Zhao *et al.* (2019) meta-analysis of 33 cohort studies found a marked significant inverse association (HR 0.88, 0.80-0.96). This variation could be due to the increased number of study populations that was included in Zhao *et al.* (2019)

meta-analysis as compared to the study populations included in the He *et al.* (2004) and Xun *et al.* (2012) meta-analyses.

Recently published cohort studies confirmed the inverse association of fish consumption with the risk of some type of stroke. In a cohort study involving 20,969 Mediterranean participants aged ≥35 years old with a median follow up period of 4.3 years, a 38% reduced risk of stroke (HR 0.62, 0.26-1.51) was found among participants that consumed fish ≥4times/week when compared to those with fish intake of <2times/week (Bonaccio *et al.*, 2017), but it is not statistically significant. Likewise, Hengeveld *et al.* (2018) EPIC-Netherlands 18-years follow-up cohort study found a reduced risk of ischaemic stroke among 34,033 Dutch participants aged 20-70 years that consumed ≥1 serving per week of lean and fatty fish with (HR 0.70, 0.57-0.86) and 0.63 (0.39-1.02) respectively, while consumption of <1 serving/week of total, fatty, or lean fish showed no association with any CVD outcome, including stroke, CHD, MI, when compared with non-fish consumers. However, a conflicting result was found in a recent U.S veteran's prospective cohort study of 508,699 participants aged ≥ 66 years old, which showed no consistent association of the risk of stroke across all the fish consumption level (Ward *et al.*, 2018). Likewise, a non-significant association of total fish, fatty fish and lean fish was found with the risk of stroke in both the male and female participants in a Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain) study of 41,020 male and female participants aged 20-69 years with a mean follow-up period of 13.8 years (Amiano *et al.*, 2016). The variation in the findings of the individual studies could be explained by the possible existence of reverse causation, which arises when the occurrence of disease affects and changes the food consumption habits of individuals. It could also be due to the variation in the studies sample sizes, the length of follow-up, the type of fish assessed, the fish preparation method and the adjusted confounding variables in each of the studies.

In summary, the evidence gathered from all meta-analyses of prospective cohort studies suggests an inverse association of fish consumption with the risk of stroke, most especially with ischaemic stroke. Therefore, this indicates a convincing favourable effect of the impact of fish consumption on the risk of some stroke subtype.

2.4 Fish Consumption and Respiratory Diseases

Respiratory diseases including chronic obstructive pulmonary disease (COPD) have emerged as one of the world leading causes of morbidity and mortality (López-Campos, Tan and Soriano, 2016; WHO, 2018). Dietary intake such as the consumption of fish is gradually attracting recognition as modifiable modulator of chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma. Emerging evidence has shown the beneficial role of fish consumption on the risk of respiratory diseases (Smit *et al.*, 1999).

2.4.1 Chronic Obstructive Pulmonary Disease (COPD)

It was estimated that by the year 2020, Chronic Obstructive pulmonary disease (COPD) will be the third world leading cause of morbidity and mortality (López-Campos, Tan and Soriano, 2016; WHO, 2018). Evidence has shown the beneficial role of fish consumption on the risk of COPD, but with limited data. Shahar *et al.* (1994) atherosclerotic risk in communities' study (ARIC) involving 8960 former or current smokers aged 45-64 years old found an inverse association of the risk of three defined COPD cases; when the highest quartile of the dietary intake of omega-3 fatty acids (median intake of 4 servings of fish/week) was compared with its lowest quartile, odd ratio (OR) was 0.66 (0.52-0.85), 0.31 (0.18-0.52) and 0.50 (0.32-0.79) for chronic bronchitis, physician-diagnosed emphysema and spirometrically detected COPD respectively (Shahar *et al.*, 1994). The significant inverse association of dietary intake of omega-3 fatty acids with COPD was maintained; when all three COPD cases were analysed together, OR was 0.59 (0.46-0.79) (Shahar *et al.*, 1994). This study was supported by Smit *et al.* (1999) review including several large observational studies with older participants, where a protective effect of higher fish consumption on the risk of lung function was suggested. This review was supported by a cohort study. Varraso *et al.* (2014) Nurses' Health Study and Health Professionals Follow-Up study involving 120,175 male and female participants aged 30-75 years with a follow up period of 16 years found a 29% significant reduction in the risk of COPD with (adjusted HR 0.71, 0.54-0.94) when the highest fish consumption level of ≥4 servings/week was compared with the lowest fish consumption level of <1 serving/week.

In summary, the findings of these studies suggest a convincing beneficial effect of higher fish consumption on the risk of COPD.

2.4.2 Asthma

Asthma is one of the most common chronic non-communicable diseases worldwide (Braman, 2006). Asthma can be influenced by environmental factors including nutrition (Mckeever and Britton, 2004). Several studies have demonstrated the beneficial role of fish consumption on the risk of some respiratory disease (e.g. asthma) (Yang *et al.*, 2013). However, these studies have conflicting findings. A European nested case-control study involving 105 cases and 420 controls aged 35-65 years old found a non-significant reduced risk of asthma among participants that had a higher fish consumption with (adjusted OR 0.93, 0.54-1.59) when compared to those with the lowest consumption (Nagel and Linseisen, 2005). Similarly, an American prospective cohort study of 4,162 young adults aged 18-30years with a 20 years follow-up period found a non-significant inverse association of the risk of asthma among the highest consumers of non-fried fish compared to the lowest consumers (HR 0.89, 0.65-1.22). However, a significant inverse association of the risk of asthma was found among the participants in the highest quintile of long chain omega-3PUFA when compared to those in the lowest quintile (HR 0.46, 0.33-0.64) (Li *et al.,* 2013). When these two studies were pooled together in Yang *et al.* (2013) meta-analysis including three adult cohort studies, two of the studies with fish consumption data, found a non-statistically significant association of the risk of asthma among the participants with the highest consumption of fish compared to those with the lowest consumption (RR 0.90, 0.69-1.18). Similar findings (RR 0.70, 0.46-1.05) were found in the three studies that reported LC omega-3PUFA intake when the highest quintile was compared to the lowest quintile. Conversely, Kim and Ju (2019) Korean cross-sectional study of 13,038 participants aged 19-64 years found a 37% significant reduction in the risk of doctor-diagnosed asthma (OR 0.63, 0.41-0.97) when the highest quartiles of fish consumption were compared with the lowest quartile, while a non-significant association was found among the medication-prescribed asthma participants and highest quartiles of fish consumption, when compared with the lowest.

Overall, the available data shows a reduction in the risk of asthma with higher consumption of fish, though not all are significant. Therefore, due to the small number of studies, a possible protective effect of higher fish consumption was found with the risk of asthma, which needs further research.

2.5 Fish Consumption and Cancer

Globally, cancer is one of the most common chronic non-communicable diseases with an estimation of 18.1 million new cases in 2018 (Ferlay *et al.,* 2019). Epidemiological studies that assessed the association between fish consumption and the risk of some types of cancers (e.g.

breast, prostate, colorectal, lung and gastric cancer) have indicated a protective effect. This could be due to the presence of omega-3 PUFA, a fish component that possesses anti-inflammatory and anticarcinogenic properties which encourages mutation suppression, cell growth inhibition, and cell apoptosis enhancement (Karmali, 1989; Rose and Connolly, 1999).

Below are summaries of studies on fish consumption and the risk of some types of cancer with reference to existing meta-analyses and recent studies.

2.5.1 Breast Cancer

Breast cancer is one of the world leading causes of mortality among the female population (Ferlay *et al.,* 2013). Modifiable risk factors among which is diet have been associated with its risk reduction. Evidence from several epidemiological studies has shown a protective effect of fish consumption on the risk of breast cancer, but with inconclusive findings. Zheng *et al.* (2013) meta-analysis of 26 prospective cohort studies (21 independent cohorts) including 883,585 participants and 20,905 breast cancer cases of which 11 cohorts (687,770 participants and 13,323 breast cancer cases) assessed the association between fish consumption and the risk of breast cancer found no association (RR 1.03, 0.93-1.14). However, when the 17 studies (16 independent cohorts) that examined the association between marine omega-3 PUFA (a fish component) and the risk of breast cancer were pooled together, they found a 14% significant reduction (RR 0.86, 0.78-0.94) in the risk of breast cancer when the highest category of fish consumption was compared with the lowest category of consumption (Zheng *et al.,* 2013). Although some of the studies included in this meta-analysis showed a reverse relationship between fish consumption and breast cancer, their pooled analysis with other studies showed no association (Zheng *et al.,* 2013). A Japanese prospective cohort study of 14.1years follow-up period including 38,234 female participants aged 45-74 years found no association of total fish consumption and total omega-3 PUFA on the risk of breast cancer (HR 0.99, 0.77-1.28) and 0.99 (0.76-1.28) (Kiyabu *et al.*, 2015). Zhihui *et al.* (2016) meta-analysis of 27 observational studies found a non-significant inverse association of the risk of breast cancer when the highest fish consumption level was compared with the lowest fish consumption (RR 0.96, 0.87-1.07). Conversely, a recently published meta-analysis of 11 studies of 130,365 Asian patients found a significant reduction in the risk of breast cancer with increased consumption of omega-3 fatty acids in fish (OR 0.80, 0.73-0.87) (Nindrea *et al.,* 2019).

The differences in the study findings could be due to the variations in the studies' sample sizes, geographical location, the length of follow-up, the types of fish assessed, cooking methods and the confounders adjusted in each of the study.

Overall, an association of fish consumption on the risk of breast cancer was apparent in some of the previous independent studies assessing the risk of breast cancer and fish consumption, thus suggesting a possible protective effect.

2.5.2 Prostate Cancer

Globally, prostate cancer is one of the top existing cancers that predispose men to both morbidity and mortality (Ferlay *et al.*, 2015). Epidemiological studies have shown a protective effect of fish consumption on the risk of prostate cancer, but with inconclusive findings. These are summarised in two previous meta-analyses. Szymanski *et al.* (2010) meta-analysis of 12 case control and 12 cohort studies found a borderline significant reduction in the risk of prostate cancer among the higher fish consumers; the case-control studies including 5,777 cases and 9,805 control participants were quantitatively assessed (OR 0.85, 0.72-1.00), while no association was found with the cohort studies of 445,820 male participants and 13,924 prostate cancers (RR 1.01, 0.90-1.14). However, when this meta-analysis was performed on four cohort studies that reported participants with prostate cancer–specific mortality, a 63% significant reduction (RR 0.37, 0.18-0.74) was found among the higher total fish consumers (Szymanski *et al.*, 2010). Another recent meta-analysis of 37 studies including 18 cohorts and 19 case-control studies with 55,401 cases of prostate cancer revealed a non-significant reduction in the risk of prostate cancer with total (RR 0.96, 0.88-1.04), when the highest fish consumption level was compared with the lowest level of consumption (Dai *et al.*, 2017). The RRs in separate meta-analysis for the case-control studies and the cohort studies were 0.90 (0.77-1.07) and 1.00 (0.92-1.08) respectively (Dai *et al.*, 2017). Conversely, a recent Danish cohort study including 27,178 male participants and 1,690 prostate cancer cases published after these meta-analyses found no association of any type fish consumption with the risk of total prostate cancer or high-grade prostate cancer (Outzen *et al.*, 2018). The variation in the findings could be due to the study sample sizes, study design, follow-up duration and type of fish assessed in the studies.

In summary, few of the pooled meta-analysis results demonstrated reduced risk of prostate cancer with the highest fish consumption level, thus indicating a possible protective effect.

2.5.3 Colorectal Cancer

Data from several epidemiological studies have shown a protective effect of fish consumption on the risk of colorectal cancer, but with inconclusive findings. These are summarised in two previous meta-analyses. Geelen *et al.* (2007) meta-analysis of 19 independent cohort studies, of which 14 cohorts examined the risk of incidence colorectal cancer in relation to fish consumption found a 12% borderline significant reduction in the risk of colorectal cancer RR 0.88 (0.78-1.00), when the highest fish consumption levels were compared with the lowest consumption level. Likewise, Wu *et al.* (2012a) meta-analysis of 41 observational studies including 22 prospective cohorts and 19 case-control studies revealed a 12% significant reduction in the risk of colorectal cancer (OR

0.88, 0.80-0.95) when the highest fish consumption levels was compared with the lowest fish consumption level. This significant reduction was maintained, when the analysis was stratified by the type of studies showing (OR 0.83, 0.72-0.95) for cohort studies, but a non-significant reduction (OR 0.93, 0.86-1.01) for the case-control studies. Yu and colleagues (2014) conducted a meta-analysis of 20 prospective cohort studies and found a significant reduction in the risk of colorectal cancer in relation to higher consumption of fish (RR 0.93, 0.87-0.99). Although some of the previously pooled studies showed an inverse association of fish consumption with the risk of colorectal cancer, other individual studies demonstrated non-inverse associations or no associations. Recently, a Chinese case-control study including 1,189 cases and 1,189 controls published after this meta-analysis found a significant reduction in the risk of colorectal cancer when the highest quartile of freshwater fish was compared with the lowest quartile (OR 0.47, 0.36-0.60) (Xu *et al.,* 2015). Similar significant reduction was found for the risk of colorectal cancer in relation to sea fish and fresh fish consumption with (OR 0.79, 0.62-0.99) and (OR 0.49, 0.38-0.62) respectively (Xu *et al.,* 2015). However, no significant association of the risk of colorectal cancer was found with dried/salted fish and shellfish consumption (Xu *et al.,* 2015). A recently published European cohort study of 521,324 participants with a median follow-up period of 14.9 years found a significant inverse association between fish consumption and the risk of colorectal cancer; adjusted HR was 0.88 (0.80-0.96) in participants with the highest quintile of total fish consumption vs the lowest quintile (Aglago *et al.*, 2020). Similar significant reduction was found in the risk of colorectal cancer in relation to fatty fish consumption (HR 0.90, 0.82-0.98), but a non-significant reduction in lean fish consumption (HR 0.91, 0.83-1.00). The discrepancies in the study findings could be partly explained by the type of fish consumed, cooking method in studies, study areas and duration of follow-up.

Overall, the pooled meta-analysis results suggested an association between fish consumption and the risk of colorectal cancer with convincing evidence.

2.5.4 Lung Cancer

The beneficial effect of fish consumption on the risk of lung cancer was apparent in various epidemiological studies. These are summarised in a previous meta-analysis. Song *et al.* (2014) meta-analysis of twenty studies including 17 case-control and 3 cohort studies with 8,799 lung cancer cases and 17,072 non-cases found a significantly reduced risk of lung cancer among participants with high consumption of fish (RR 0.79, 0.69-0.92). The subgroup analysis shows similar result among the case-control studies with (RR 0.76, 0.63-0.91), but a non-significant association among the cohort studies 0.95 (0.73-1.24) (Song *et al.*, 2014).

Overall, the pooled result indicated a protective effect of fish on the risk of lung cancer.

2.5.5 Gastric Cancer

Globally, gastric cancer is the second leading cause of mortality from cancer and the 4th frequently occurring cancer (Parkin *et al.*, 2002; Brenne *et al.*, 2009; Wu *et al.*, 2011). Data from several epidemiological studies have shown a protective effect of fish consumption on the risk of gastric cancer, but with inconclusive findings. Wu *et al.* (2011) meta-analysis of 17 studies including 15 case-control and 2 cohort studies found a non-significant reduction in the risk of gastric cancer (RR 0.87, 0.71-1.07), when the highest fish consumption levels were compared with the lowest fish consumption levels. A meta-analysis of 20 prospective cohort studies including seven cohort studies on gastric cancer showed no association of higher fish consumption with the risk of gastric cancer in the sub-group analysis (RR 1.06, 0.96-1.17) (Yu, Zou and Dong, 2014).

However, a recent dose response analyses study suggested 2%-7% reduction in the risk of gastrointestinal cancer with every 20g/day increment in fish intake which is equivalent to one portion/week (Li *et al*., 2020).

Although some of the previously pooled studies showed an inverse association of fish consumption and the risk of gastric cancer, other individual studies demonstrated non-inverse associations or no associations, which could explain the no association found when all the studies were pooled. Overall, the current pooled studies demonstrated no significant impact of fish consumption on the risk of gastric cancer, which could be due to the difference in the study designs included in the Wu *et al.* (2011) meta-analysis.

2.6 Fish Consumption and Diabetes

Several epidemiological studies that assessed the association between fish consumption and the risk of type 2 diabetes mellitus (T2D) demonstrate a protective effect. These are summarised in three previous meta-analyses of prospective cohort studies. Xun *et al.* (2012) meta-analysis of nine prospective cohort studies including 12 independent cohorts with 438,214 participants found a non-significant inverse association of higher fish consumption and the risk of diabetes with a pooled (RR 0.99, 95% CI 0.85-1.16) among the participants that ate fish ≥5 times/week when compared to those that never consumed fish or ate fish <once/month. Another meta-analysis of 16 prospective cohort studies including 527,441 participants with 24,082 diabetes cases found (RR 1.05, 1.02-1.09), 1.03 (0.96-1.11) and 0.98 (0.97-1.00) for the risk of type 2 diabetes with every increment in the servings of fish consumed per week (Wallin *et al.*, 2012). A further analysis presented a matching RR result of 1.17 (1.09-1.26), 0.98 (0.70-1.37) and 0.90 (0.82-0.98) for the risk of type 2 diabetes for every increment of 0.3g/day intake of omega-3 PUFA (Wallin *et al.*, 2012). Wu *et al.* (2012b) meta-analysis of 16 studies (18 independent cohorts) including 540,184

participants and 25,670 diabetes cases of which 13 cohorts examined the association of fish and/or seafood on the risk of incident diabetes found a non-significant association of the risk of diabetes (RR 1.12, 0.94-1.34) per 100g of fish consumed per day. However, when the studies were stratified by study location, a reduced risk of diabetes was found among the Asian studies (RR 0.89, 0.81-0.98) per 100g of fish consumed a day, while higher risk was found among the studies from North America/Europe (RR 1.38, 1.13-1.70) (Wu *et al.*, 2012b). Similarly, Zheng *et al.* (2012) meta-analysis of 24 cohort studies including 545,275 participants and 24,509 type 2 diabetes patients found (RR 1.07, 0.91-1.25) for the risk of diabetes when the highest total fish consumption category was compared with the lowest category of total fish consumption. The subgroup analyses showed a significant association of the risk of diabetes (RR 0.89, 0.81-0.98) when the highest total fish consumption category was compared with the lowest total fish consumption category among the Asian population (Zheng *et al.*, 2012). On the contrary, Zhang *et al.* (2013) published a meta-analysis of 11 prospective cohort studies of which 10 of the studies including 549,955 participants assessed the association between fish/seafood consumption and the risk of T2D and found a significant reduced risk of diabetes (RR 0.89, 0.82-0.96) with high intake of oily fish when the studies were stratified by the type of fish consumed and pooled together. The dose response meta-analysis also suggests a 20% reduction in the risk of T2D for every 80g intake of oily fish per day. However, a non-significant association (RR 0.66, 0.93-1.12) was found with lean fish consumption and the risk of T2D, and when all studies that reported the fish/seafood consumption and the risk of T2D were pooled together (RR 1.04, 0.9-1.2) (Zhang *et al.*, 2013), thus showing inconsistency in the findings. A recently published meta-analysis of 7 prospective cohort studies found a significant reduction in the risk of T2D (RR 0.89, 0.82-0.98), when the highest fatty fish intake was compared with the lowest intake (Namazi *et al.*, 2019). Nevertheless, non-significant associations were found with the consumption of lean fish, other seafood, fish products and fried fish and the risk of T2D with respective RR (1.03, 0.87-1.22), (0.95, 0.83-1.10), (0.96 0.82-1.13) and (1.02, 0.83-1.26) (Namazi *et al.*, 2019). The discrepancy in the findings could be due to the variation in the studies sample sizes, the length of follow-up, country regions, the types of fish assessed, the fish preparation method and the adjusted confounding variables in each of the studies. Even though all independent studies in the meta-analyses might have adjusted for known risk factors for T2D, there is the possibility of the presence of residual confounding factors.

Overall, the findings from the reported meta-analyses showed a possible protective effect of fish consumption on the risk of T2D in some regions of the world especially the Asian countries, with no protective effect in the included western countries. In addition, when the studies were stratified by the type of fish consumed, the protective effect of T2D was higher among the oily fish consumers. Therefore, there is possible evidence that fish consumption especially oily fish can influence the risk of developing T2D.

2.7 Fish Consumption and Mental Health

Mental health disorders including major depression and anxiety disorders are one of the leading causes of disability, morbidity and mortality (Collins *et al.*, 2011). Modifiable risk factors among which is fish consumption have been associated with its risk reduction. This could be due to the significant role omega-3 PUFAs played in modulating neurotransmission, neuroinflammation, neurogenesis and survival of the cell (Mischoulon, and Freeman, 2013). A prospective cohort study including 7,903 participants (173 depression cases, 335 anxiety cases and 4 stress cases) found a significant reduction in the risk of mental disorder with respective (OR 0.72, 0.52-0.99) for second quintile, 0.79 (0.58-1.08) for third quintile and 0.65 (0.47-0.90) for fourth quintile among participants with intake of omega-3 PUFA, while 30% significant reduction in the risk of mental disorder was also found among moderate fish consumers (3rd and 4th quintiles with 83.3 and 112g/day) (Sachez-Villegas *et al.*, 2007).

Below are the summaries of other related studies of fish consumption and the risk of some specific mental health outcome (depression and other psychiatric illnesses).

2.7.1 Depression

Several epidemiological studies that assessed the association between fish consumption and the risk of depression indicated a protective effect. This could be due to the presence of omega-3 PUFA as part of its constituents. The presence of omega-3 PUFA in the blood plasma could control the level of serotonin and dopamine in the brain (James *et al.,* 2000; Haag, 2003). It can also reduce oxidative stress found high among depressed people (Black *et al.,* 2015). These studies are summarised in two previous meta-analyses. Li and colleagues (2016) meta-analysis of 26 studies including 10 cohort and 16 cross-sectional studies with 150,278 participants observed a significant inverse association of fish consumption with the risk of depression with a pooled (RR 0.83, 95% CI 0.74-0.93) when compared to those with the lowest fish consumption. Similar significant inverse association was found in the sub-group analysis of the study design and gender (Li, Liu and Zhang, 2016). Likewise, another meta-analysis of 31 observational studies including 255,076 participants found a linear dose response significant inverse association of fish consumption with the risk of depression (RR 0.78, 0.69-0.89) (Grosso *et al.,* 2016). The inverse association was supported by two recent studies published after these two meta-analyses. In a cohort study involving 1,181 Japanese participants aged 63-82 years, Matsuoka *et al.* (2017) found a significantly reduced risk of major depressive disorder (MDD) among participants in the third quartile of fish consumption with an OR of 0.44 (0.23-0.84). Consistently, Yang and Je (2018a) Korean cross-sectional study of 9,183 participants aged 19-64 years found reduced odds of depression when the moderate "1–3 times/week" and the highest fish consumption level "≥4 times/week" was compared with the lowest fish consumption level "<1 time/week" with (OR 0.76, 0.56-1.04) and 0.52 (0.37-0.74) respectively. There was a stronger association of fish consumption with the risk of depression among the female participants with (OR 0.44, 0.29-0.67), while a non-significant association was found among the male participants (Yang and Je, 2018a). Another recent meta-analysis of 10 prospective cohort studies of 109,764 participants found a similar significant inverse association of fish consumption with the risk of depression when the highest level of fish consumption was compared with the lowest level with (RR 0.89, 0.80-0.99) (Yang, Kim and Je, 2018b). Sharifan, Hosseini and Sharifan (2017) randomised control trial (RCT) of 180 Iranian participants aged ≥55 years also found a significant reduction in the risk of depression after adjusting for potential confounding variables over a 6-month trial period. Although most of the pooled studies showed an inverse association of fish consumption on the risk of depression, some individual studies still demonstrated non-inverse or no association (Lucas *et al.,* 2011; Albanese *et al.,* 2012).

Overall, all the pooled studies and the interventional study showed significant protective effect of fish consumption on the risk of depression, confirming that increased consumption of fish reduces the risk of depression with convincing evidence.

2.7.2 Other Psychiatric Illness

Studies have shown the protective effect of fish consumption on the risk of some psychiatric illness e.g. anxiety disorder and cognition. This could be due to the beneficial and psychotropic effects of the omega-3 PUFAs, a fish component that in addition has anti-inflammatory and anti-oxidative properties.

2.7.2.1 Anxiety Disorder

Jacka *et al.* (2013) Australian cross-sectional study of 935 female participants aged 20-93 years found a 51% significantly reduced odds of anxiety disorders (OR 0.49, 0.24-0.98) when the highest tertile of DHA consumption was compared with the lowest tertile of consumption. A non-significant reduction in the risk of anxiety disorders (OR 0.62, 0.32-1.21) was found with the consumption of EPA, while no association was found between the consumption of fish and the risk of anxiety disorders (Jacka *et al.*, 2013). Recently a Brazilian cross-sectional study of 12,268 participants aged 35-74 years found a significant reduction in the risk of anxiety disorders among participants with the highest intake (5^{th} quintile) of DHA (OR 0.83, 0.69-0.98) and EPA (OR 0.82, 0.69-0.98) (Natacci *et al.*, 2018).

Although the available evidence of fish consumption and anxiety disorders are mainly cross-sectional design with difficulty in establishing a causal association, it still demonstrated a possible evidence of the beneficial effect of fish components on anxiety disorder. In summary, the result suggests a protective effect of the components of fish (DHA and EPA) on the risk of anxiety disorders.

2.7.2.2 Cognition

Studies have shown the protective effect of fish consumption on the risk of cognitive decline with inconsistent findings. A women's health prospective cohort study of 5,988 participants with mean aged 72 years found that over a period of 4 years higher consumption of tuna and dark-meat fish of "≥once weekly" was significantly associated with lower decline in verbal memory, when compared with <once-weekly tuna and dark-meat fish consumption (Kim *et al.*, 2013). Correspondingly, Kesse-Guyot *et al.* (2011) 13 years prospective cohort study of 3294 participants

aged 35-60 years found a borderline significant reduction in the risk of having cognitive difficulties when the highest fish consumption level was compared with the lowest fish consumption level OR 0.80 (0.63-1.01). This resonates with Qin *et al.* (2014) prospective cohort study of 1,566 Chinese participants aged ≥55 years with a mean follow-up period 5.3 years, which found a reduced global cognitive decline and slower decline in composite and verbal memory scores when the highest fish consumption level "≥1 serving/week" was compared with the lowest fish consumption level of "<1 serving/week" among participants aged ≥65years. On the other hand, no association was found among participants aged 55-64 years (Qin *et al.,* 2014). Also, the Dutch Doetinchem Cohort Study of 2,612 male and female participants aged 43-70 years found no consistent association of fatty fish consumption and cognitive decline over a 5 years follow-up period, while increased intake of omega-3 PUFA specifically a-linolenic acid (ALA) was associated with slower cognitive decline in memory and global cognition (Nooyens *et al.,* 2018). A recently published meta-analysis of 5 prospective cohort studies including one French and four US studies with 23,688 white participants aged ≥65 years with a median follow-up period ranging from 3.9-9.1 years found that higher fish consumption was associated with slower decline in both global cognition and memory (Samieri *et al.,* 2018).

The variations in the findings above could be attributed to the length of follow-up, sample sizes of the studies, the type of fish assessed, age difference, regional differences, the fish preparation method and the adjusted confounding variables in each of the studies.

Overall, the results demonstrated a protective effect of fish consumption on the risk of cognitive decline.

2.8 Fish Consumption and All-cause Mortality

Several epidemiological studies that explored the association between fish consumption and the risk of all-cause mortality indicated a protective effect. Zhao *et al.* (2016) meta-analysis of 12 prospective cohort studies including 672,389 participants and 57,641 deaths found a 6% significant reduction in the risk of all-cause mortality among participants with a higher consumption of fish (RR 0.94, 0.90-0.98) when compared to those with the lowest fish consumption. The dose response data analysis showed a 12% significant reduction in the risk of total death (RR 0.88, 0.83-0.93) among the participants that consumed 60g of fish/day (Zhao *et al.,* 2016). Another meta-analysis of 23 prospective cohort studies with 22 studies including 985,126 participants found a significant reduction in the risk of all-cause mortality (RR 0.94, 95% CI 0.90-0.98) among participants with a higher consumption of fish (Wan *et al.,* 2017). A recent umbrella meta-analyses review of prospective observational studies also found a significant reduction in the risk of all-cause mortality summary relative risk (SRR 0.92, 95% CI 0.87-0.97) among participants with 100g/day increase in fish consumption level (Jayedi and Shab-Bidar, 2020). Conversely, Jayedi *et al.* (2018) performed a meta-analysis of 14 prospective observational studies including 911,348 participants with 75,451 incident deaths and found a borderline significant inverse association with the risk of all-cause mortality (RR 0.98, 0.97-1.00) among participants with 20g/day increase in fish consumption level. On the other hand, a recently published US National Institutes of Health (NIH)-AARP diet and Health cohort study of 421,309 participants with 85,112 deaths in a follow up period of 16 years found a significant reduction in the risk of total mortality, when the highest quintile of fish consumption was compared with the lowest quintile (HR 0.91, 0.89-0.94 in men and 0.92, 0.88-0.95 in women) (Zhang *et al.,* 2018). In another recently published cohort study involving 14,117 Chinese and 33,221 US older population from the China Health and Nutrition survey (CHNS) and the National Health and Nutrition Examination survey (NHANES) with a median follow up period of 14 and 9.8 years respectively, Zhuang *et al.* (2018) found a significant reduction in the risk of total mortality among Chinese adults with increasing fish consumption levels with respective HR 0.45 (0.36-0.56) for low consumption; 0.72 (0.60-0.86) for middle consumption; and 0.70 (0.59-0.85) for high consumption of fish. On the contrary, no association of fish consumption and the risk of total mortality were found among the US adult population indicating a regional influence in the findings (Zhuang *et al.,* 2018). No significant association of fish consumption and the risk of all-cause mortality was also found in a cohort study of 1,054 male and female participants aged 60-79 years at baseline with mean follow up period of 11.7 years (HR 1.20, 0.89-1.63) (Otsuka *et al.,* 2019). Similarly, a recently published Danish cohort study of 27,178 male participants found no association of the risk of all-cause mortality and any type of fish consumption (Outzen *et al.*, 2018).

The discrepancies in the findings could be attributed to the different cooking techniques in the countries, since fish is popularly deep-fried in the Western regions while grilling and steaming are popular with the Asians. This deep-frying could negatively impact on the protective effects of the constituents in fish through trans-fatty acids production. Likewise, the various types of fish consumed in countries do have different biological and nutritional composition, which could have impact on the association. Also, the variations in the studies sample sizes and the length of follow-up could be other reasons for the discrepancies in the findings of the studies.

The significant reduction in the risk of all-cause mortality was also influenced by differences in gender. A Swedish cohort study including 72,522 male and female participants aged 45-83years with a follow-up period of 17 years found a 25% higher mortality risk among the female participants that had a lower level of fish consumption when compared with the median level of fish consumption (HR 1.25, 95% 1.11-1.40). Also, a 19% higher mortality risk was found among the male participants with lower fish consumption level (HR 1.19, 1.07-1.32) (Bellavia, Larsson and Wolk, 2017). Conversely, a 39% higher mortality risk was found among only the female participants with the highest fish consumption level (HR 1.39, 1.15-1.68) (Bellavia, Larsson and Wolk, 2017).

In summary, the pooled results demonstrated a protective effect of fish consumption on the risk of all-cause mortality, although different results might occur due to regional or gender differences.

Since all the above literatures suggest some established associations of fish consumption with chronic diseases such as CVD, certain cancer types, T2D, depression, respiratory disease, and all-cause mortality, which is due to their omega-3 PUFAs constituent that exhibit anti-inflammatory, anti-atherosclerotic, antithrombotic, anti-arrithymic properties, it is hypothesized that fish consumption will be associated with the risk of dementia. As this is the focus of this research, the following sections will explore the epidemiology of dementia and the existing studies that have reported the association of fish consumption with the risk of dementia, and the factors influencing the consumption of fish with detailed explanation of the conceptual framework adopted in this study.

2.9 Dementia Epidemiology and Association of Fish consumption with Dementia

Due to significant increase in life expectancy and population ageing in the world (currently estimated at 900 million people ≥60 years old: Prince *et al.*, 2015), there will be rapid increase in the prevalence of chronic non-communicable diseases among which is dementia, that constitute the major cause of their morbidity and mortality (WHO, 2015) and hence the focus of this thesis.

Preserving a good cognitive function throughout the life course is crucial for effective aging (Uauy and Dangour, 2006). This cognitive maintenance is paramount at old age to safeguard all independent daily activity task and quality of life of the aged. Hence, it is important to appreciate the existence of this chronic disease such as dementia and find ways to interrupt or prevent its manifestation at old age, since its incidence and prevalence rises as age increases (Lobo *et al.*, 2000; Fratiglioni *et al.*, 2000).

The overarching theme of this thesis is to explore one of the dietary factors (fish consumption) that could reduce the risk of dementia including Alzheimer's disease and the determinants that could hinder its adequate consumption.

This part of the review will explore the epidemiology of dementia: its clinical symptoms, incidence, prevalence, prognosis, cost and risk factors, and the existing evidence on the association of fish consumption on the risk of dementia including AD with reference to existing meta-analysis of human epidemiological studies. In addition, the factors influencing the consumption of fish and the conceptual framework employed in this thesis will be explored.

2.9.1 The Epidemiology of Dementia

2.9.1.1 Definition and Clinical Symptoms of Dementia

Dementia is a neurodegenerative chronic disorder that affects the proper functioning of the cognitive part of the brain (WHO, 2019). It is a term used to express irreversible progressive degenerative changes in the brain (WHO, 2019). It is a syndrome that is common with older adult but not necessarily a disease ascribed only to the elderly (WHO, 2019). This chronic disorder manifests due to several types of conditions that have a primary or secondary impact on normal brain functioning e.g. Alzheimer's disease or stroke or negative effect of substance use and not necessarily the effect of an age-related memory loss (WHO, 2019). This disease is characterised by the manifestation of multiple cognitive dysfunction which include memory decline (Amnesia) and one or more of these cognitive disturbances such as aphasia (language), apraxia (tasks), agnosia (pattern recognition), and executive functioning (decisions/planning) (Beydoun *et al.*, 2014). This syndrome has different sub-categories, among which is Alzheimer's disease (AD) that account for 50-70% of all types of dementia with a prevalence increase of 1% among people aged <60 years old to 40% among people aged >85 years old (Qiu *et al.,* 2009; Beydoun *et al.*, 2014; WHO, 2019). AD is a multifactorial disease that is characterised by three neuropathological hallmark proteins. These include the extracellular plagues of β-amyloid protein (amyloid plagues) enclosed by dystrophic neurites, intracellular neurofibrillary tangles (NFTs) and neuronal degeneration (Reitz *et al.*, 2011; Alzheimer's Association, 2016). All these progressively develop and degenerate the brain thereby leading to neuronal cell death due to shrinkage of different parts of the brain, which subsequently causes cognitive disorders and later dementia (Jack *et al.*, 2010; Jack *et al.*, 2013; Alzheimer's Association, 2016). Other types of dementia include vascular dementia (VD) the second most common subtype of dementia which occur after stroke or transient ischemic attack (TIA) accounting for 15-25% of all cases of dementia; dementia with Lewy-bodies (DLB) with symptoms of Parkinsonism, visual hallucinations attention and problem solving deficits in patients; frontotemporal dementia (FTD) with symptoms of executive dysfunction, disinhibition and apathy, and lastly mixed dementia (MD) with evidence of more than one causes of dementia (Jiang *et al.,* 2013; Foltyn, 2015; Alzheimer's Association Report, 2016).

Dementia symptoms vary among people. This progressively deteriorates the cognitive and functional capability of the affected individual. These symptoms involve deterioration of individual learning skills, memory, thinking, understanding, orientation, judgement and verbal communication with total reliant on the aetiology and the affected region of the brain, but have no effect on their state of consciousness (WHO, 2019). At the initial stage of the disease, a short-term loss in memory emanates at the hippocampus and the temporal lobe of the brain. This presents as slight forgetfulness and becomes obvious as the brain degeneration progresses due to extensive brain atrophy resulting from destruction of nerve cells (neurons) (Alzheimer's Association, 2016). The difficulties in reminiscences and making right decision, carrying out daily household tasks, having slight confusion and being less motivated also accompany this preliminary stage. As the disease progresses, the regions of the brain that involve logical reasoning, skilled movements and ability to recognise are affected (Morrison and lykestos, 2005). Afterwards, this degenerate to inability to independently perform personal hygiene, which makes them to be totally dependent on others. Mood swing and some behavioural changes such as wandering might set in as the progression continues into the later stage of the disease (Morrison and lykestos, 2005). In the severe stage of the disease, the affected individual loses their talking and language skills, and becomes susceptible to continuous support in executing all their daily activities of personal hygiene and feeding (Alzheimer's Association, 2016; WHO, 2019).

Various methods of assessment can be used to diagnose dementia and its subtypes. This requires a cautious and comprehensive clinical investigation. A physician and neurological expert will obtain information about the medical and family history of the patient. These include information about the patient psychological state, and the patient history of psychiatric, cognitive and behavioural changes (Alzheimer's Association, 2016). Blood test and neuroimaging using the magnetic resonance imaging (MRI) might also be conducted during the diagnosis to ensure other potential causes are eliminated and to further expose other valuable information about some of the disease features (Alzheimer's Association, 2016).

2.9.1.2 Prevalence and Incidence of Dementia

According to the 2015 World Alzheimer's Report, 46.8 million people in the world were estimated to be living with dementia, with an increment of twice the figure every 20 years and a prediction of 131.5 million cases by the year 2050 (Prince *et al.,* 2015). Most of the increment is expected to be in the Low- and middle-income countries (LMICs), which currently hold 58% of the people living with dementia and is projected to rise to 63% by 2030 and 68% by the year 2050 (Prince *et al.,* 2015). Nearly half of the people living with dementia estimated at 22.9 million were found in Asia in 2015. This is more than the combination of the dementia population in the European region and the United States of America (USA) of 10.5 million and 9.4 million respectively (Prince *et al.,* 2015). Furthermore, globally, over 9.9 million incidence cases of dementia were estimated to occur annually in 2015, which signifies one new dementia case every 3.2 seconds (Prince *et al.,* 2015), thus making dementia an important public health problem (WHO, 2015).

2.9.1.3 Risk Factors for Dementia

Evidence from epidemiological studies declares that the risk factors that influence the development of cognitive impairment or dementia include the non-modifiable factors (e.g. age and genetic), and lifestyle, environmental, psychosocial, and nutritional factors that are modifiable (Qiu *et al.,* 2007; Qiu *et al.,* 2009; Baumgart *et al.,* 2015). Since the non-modifiable risk factors are unchangeable, strategy needed for the prevention of dementia should focus on the modifiable risk factors that are amendable among which is fish consumption, a nutritional factor that is associated with the risk of dementia, but the existing results are currently inconsistent.

Fish consumption is a significant part of human nutrition with valuable nutrients that directly maintain human health and indirectly prevent chronic diseases such as cardiovascular diseases which is linked to cognitive impairment. Fish consumption has contributed immensely to the prevention of chronic diseases over the years (Xun *et al.*, 2012; Zheng *et al.*, 2012), because of its long chain omega-3 polyunsaturated fatty acids (PUFAs) constituent that comprise of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Long chain omega-3PUFAs have neuroprotective properties and plays role in the brain and vascular system through several mechanisms of action. They improve the endothelial function and blood flow to the brain (Tsukada *et al.*, 2000; Wang *et al.*, 2012). They restrict the production and buildup of the β-amyloid peptide toxin and suppress numerous transduction pathways signal (Cole *et al.*, 2009). They decrease inflammation through their anti-inflammatory properties by impeding leukocyte migration, prevent the conversion of arachidonic acid to proinflammatory factors (Gil, 2002), since inflammation influences the pathophysiology of dementia (Akiayama *et al.*, 2000; Heppner, Ransohoff and Becher, 2015).

2.9.1.4 Prognosis of Dementia

Dementia is a chronic disease with an estimated mortality risk which is at least two times higher than people without dementia (Dewey and Saz, 2001). It is a disease known with poor prognosis (Van De Vorst *et al.*, 2015). In the nearest future, dementia is predicted to be one of the leading causes of mortality, hence outpacing cardiovascular diseases (James *et al.*, 2014; Weuve *et al.*, 2014). Several studies have shown the relationship of dementia with the risk of mortality. This was observed in a review by Guehne *et al.* (2005) that found all types of dementia were significantly associated with an increase in the risk of mortality. A prospective cohort study of 1670 participants aged ≥65 years old and 15 years follow-up period found 40% significant increase risk of mortality among AD participants when compared with those without AD (HR 1.4, 95% CI 1.2-1.8) when all the whole participants were analysed (Ganguli *et al.*, 2005). When the analysis was stratified with sex, the increase in mortality risk was significantly maintained among the female participants (HR 1.7, 1.3-2.2) but non-significant among the male participants (HR 1.2, 0.9-1.7) (Ganguli *et al.*, 2005). In a Dutch cohort study involving 59,201 participants, Van De Vorst *et al.* (2015) reported higher mortality risk among the participants with dementia, compared to those without dementia.

2.9.1.5 Outcomes and Cost of Dementia

The financial implication of dementia worldwide was estimated has $818 billion. This is expected to increase to a trillion dollar by the year 2018 and 2 trillion dollar by 2030 (Prince *et al.*, 2015). This significantly influences the direct medical costs of treating dementia and other conditions in primary and secondary care. It also affects the social and the informal care costs of unpaid care provided by family and others and those provided by community care specialists. The estimated dementia costs are currently significant, and there is prediction of a predominant rise in the low and middle-income countries (LMICs), where a noticeable increase in the number of the aged population is expected to occur resulting into a rise in the number of people with dementia (Wimo *et al.*, 1997; Qiu *et al.*, 2009). Due to a drastic increase in the number of people afflicted with dementia, there is expected to be a proportionate rise in the cost of care. This financial burden coupled with an increase in the number of the aged population could negatively impact on the future social care need and the health systems, especially in the LMIC, hence the need for dementia prevention.

2.9.2 Association of Fish Consumption with Dementia

2.9.2.1 Impact of Fish Consumption on Incident Dementia

The evidence that shows the impact of fish consumption on incident dementia are summarised in four existing meta-analyses of cohort studies (Wu *et al.*, 2015; Cao *et al.*, 2016; Zhang *et al.*, 2016; Zeng *et al.*, 2017). Wu *et al.* (2015) meta-analysis of 6 cohort studies including 22,402 participants showed a statistically significant reduction in the risk of AD with pooled (RR 0.64, 0.44-0.92) among higher fish consumers when compared with the lower fish consumers. However, when five of these cohort studies that reported incident dementia were examined, a marginally significant reduction in the risk of dementia (RR 0.84, 0.71-1.01) was found among higher fish consumers when compared with the lower fish consumers (Wu *et al.*, 2015). Cao *et al.* (2016) meta-analyses of 43 studies, of which four cohorts examined the association of fish consumption with the risk of dementia found a non-significant reduction in the risk of dementia (RR 0.79, 0.59-1.06) among the fish consumers when compared to the non-consumers. In the dose response meta-analysis by Zhang *et al.* (2016) including 21 cohort studies of which four studies examined the risk of both dementia and AD, an increment of 1 serving/week of fish consumption showed a 5% reduced risk of dementia (RR 0.95, 0.90-0.99) and 7% reduced risk of AD (RR 0.93, 0.90-0.95). Similarly, Zeng *et al.* (2017) meta-analysis of 9 cohort studies including 28,754 participants found a 20% significant reduction in the risk of AD (RR 0.80, 0.65-0.97) when the highest level of fish consumption was compared with the lowest level, although the matched figure for dementia was not statistically significant (RR 0.86, 0.73-1.02). On the other hand, a recently published Three-City cohort study of 5934 participants aged ≥65 years with a mean follow-up period of 9.8 years and 662 dementia cases found no significant association of fish consumption and the risk of dementia and AD with HR 1.09 (0.72-1.67) and 1.06 (0.65-1.75) respectively, when the highest fish consumption frequency of ≥4 times/week was compared with the lowest frequency of consumption of <1 time/week (Ngabirano *et al.*, 2019).

Although a preponderant number of previously pooled studies have shown an inverse association of fish consumption with the risk of dementia, some independent studies still displayed no association or a borderline, non-significant inverse association, hence showing inconsistent results till date. However, the notable variance in the findings of these individual studies could be ascribed to several issues that could be explained by considering the specific type of fish consumed in different countries, since they have different biological and nutritional composition, which could have affected the impact of the association. Other issues could be attributed to the duration of exposure to fish consumption, selection and information bias, sample sizes, dosage of fish consumption, adjustments for confounders, genetic susceptibility, attrition rate and the possibility of reverse causation since the pathophysiology of dementia/AD start 10 to 20 years before the actual clinical manifestation of the disease (Amieva *et al.*, 2008).

Overall, majority of the pooled meta-analyses results suggest a protective effect of fish consumption on the risk of dementia, but the literature from the current studies has suggested inconsistencies in their findings and the association of increased fish consumption with reduced risk of dementia requires further research.

2.9.2.2 Impact of Fish Consumption on Dementia Prognosis

Few studies have shown the association of fish consumption with dementia prognosis. This was observed in a recent US prospective cohort study of 421,309 participants aged 50-71 years and 85,112 total deaths with 16 years follow up period that found a significant inverse association between fish consumption and Alzheimer's disease mortality (Zhang *et al.*, 2018). Similarly, Zhuang *et al.* (2018) cohort study of 33,221 US adult population found 63% reduced risk of mortality from Alzheimer's disease among the highest fish consumers. Further studies are required to examine the association of fish consumption with mortality in people with dementia, being one of the prognoses of dementia.

2.9.3 Factors Influencing the Consumption of Fish

Although several studies have investigated the factors that influence the consumption of fish, there is limited data on the factors influencing the consumption of fish primarily in older people. Most of these studies were based on participants of diverse age-group, while some studies included only female participants (Trondsen *et al.*, 2003; Trondsen *et al.*, 2004). Among these studies few have examined the factors influencing the consumption of fish in older people. An Australian cross-sectional study of 854 participants aged ≥ 51 years old reported cost of fish as the most occurring factor that affected the increase in fin-fish consumption among participants that have large household size, (Greiger, Miller and Cobiac, 2012). Myrland *et al.* (2000) Norwegian cross-sectional women study of 11,000 participants aged 30-44 years acknowledged that the level of fish consumption was increased with age, household size, and higher educational level. Similarly, Pieniak *et al.* (2010) European cross-sectional study of 4,786 participants aged 18-84 years showed that participants that had better knowledge about fish, were highly educated and interested in eating healthy were more likely to regularly consume fish. Another Norwegian women study of 9,407 participants aged 45-69 years also acknowledged poor quality, high price and lack of availability of fresh fish as a barrier that hinder the consumption of fish (Trondsen *et al.*, 2003). Birch *et al.* (2012) acknowledged convenience as one of the factors that influence the consumption of fish. Correspondingly, other existing studies that reported factors that positively or negatively influence fish consumption was acknowledged in a systematic review of 49 studies where a conceptual framework (see Fig 2.1) was developed to accommodate all the enablers/drivers and barriers of fish consumption that are the positive and negative influencing factors affecting the frequency of fish consumption and connected via two parallel pathways (Carlucci *et al.*, 2015).

2.9.3.1 Conceptual Frameworks

Carlucci *et al.* (2015) framework demonstrates how peoples' personal (values, beliefs, attitudes and demographics), situational and environmental factors in a contextual situation can influence the consumption of fish, especially those factors relating to the quantity and frequency of fish consumption and other pertinent fish products quality and characteristics considered during their selection. This framework shows how choice in relation to the frequency of fish consumption and the quality of fish is facilitated by both the drivers and barriers of fish consumption. In this conceptual framework, other factors including sensory perception, perceived health benefits, fish eating habits, convenience perception, self-efficacy during fish preparation, high price, availability of fish, and inadequate knowledge to choose and prepare fish were highlighted as very crucial enablers/drivers and barriers of fish consumption that could positively or negatively influence the consumption of fish (Carlucci *et al.*, 2015). These factors will be briefly discussed in the followings.

Figure 2.1: Conceptual Framework on Factors Influencing the Consumption of Fish (Adopted from Carlucci et al., 2015)

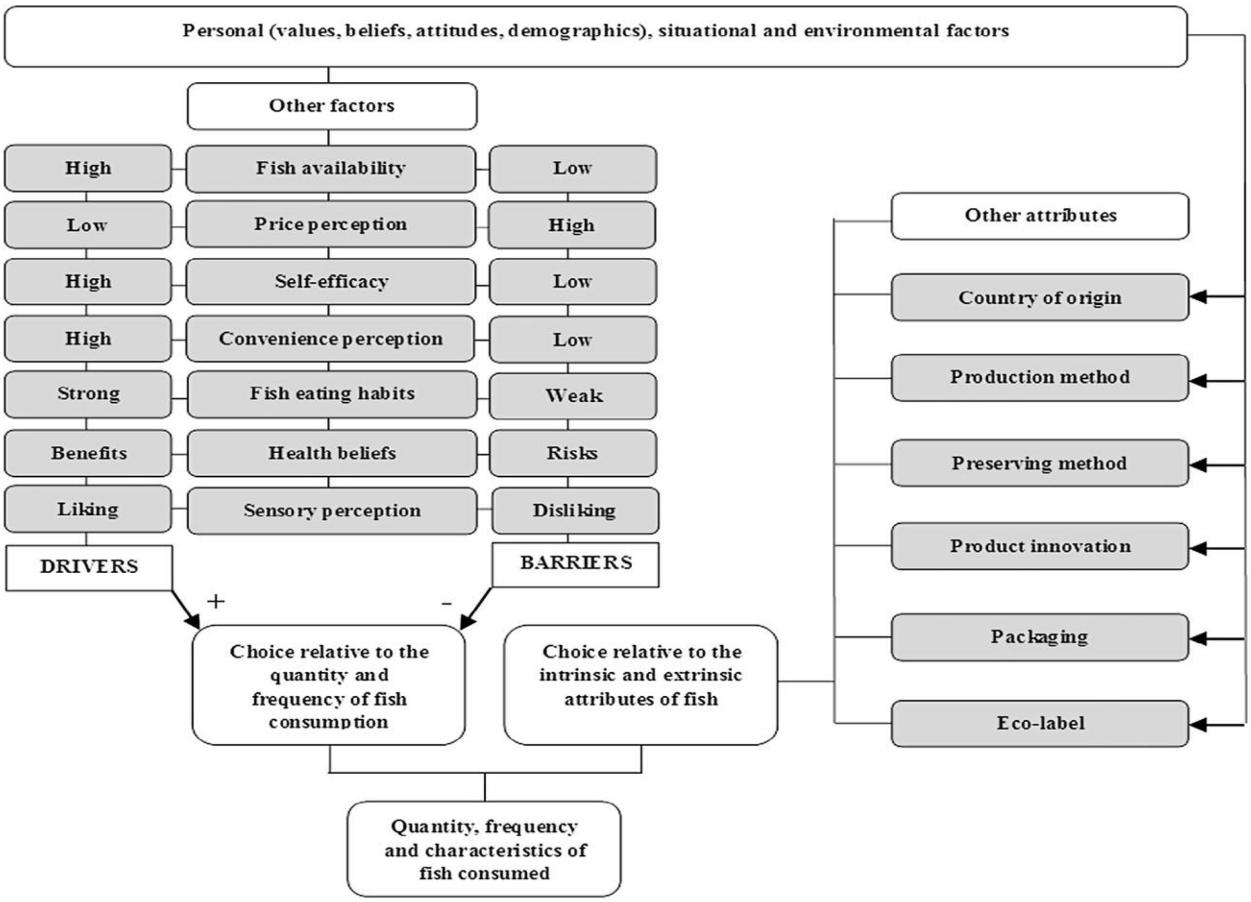


Figure 2.1: Conceptual Framework on Factors Influencing the Consumption of Fish (Adopted from Carlucci *et al.*, 2015).

2.9.3.1.1 Socio-demographic factors

Previous studies have examined several socio-demographic characteristics influencing the consumption of fish with various findings. Age was acknowledged as a factor that significantly influences the frequency of fish consumption. There was evidence from a large population-based cross-sectional study of 9250 older adults aged ≥65years that reported infrequent fish consumption among the older participants (Larrieu *et al.*, 2004a). Conversely, a Norwegian cross-sectional study of 9407 participants aged 45-69 years observed that increase in age was associated with fish consumption (Trondsen *et al.*, 2004).

Gender was reported in previous studies as a factor that influences the rate of fish consumption. Men were reported to have increased consumption of fish than women (Johansson *et al.,* 1998). This was seen in a Norwegian cross-sectional study of 3144 participants aged 16-79 years that found an increased daily intake of fish among men (Johansson *et al.,* 1998). A cross-sectional study of 1200 participants aged 14-71 years in Taiwan found a significantly reduced odds of fish consumption (OR 0.71) among women (Li *et al.,* 2001). This corroborates with the findings of Wenaty *et al.* (2018) Tanzanian cross-sectional study of 122 participants that reported higher fish consumption among their male participants than female participants. However, a Turkish cross-sectional study of 127 randomly selected participants found that the females' yearly fish intake level was 1.19 kg more than the male participants' intake level (Can, Günlü and Can, 2015). The discrepancies in the findings of these studies could be that women are more likely to be financially incapacitated, therefore affecting the rate at which fish products are purchased. This in turn may impact on the frequency of fish consumption. It could also be that men usually eat better meals outsides than inside their homes.

Educational level was acknowledged in several studies as a socio-economic factor that predicts the frequency of fish consumption. It was demonstrated in an Australian cross-sectional study of 854 participants that found an increase in fresh finfish and canned fish consumption level among older participants aged ≥51 years with higher educational level (Grieger, Miller and Cobiac, 2012). A French cross-sectional study also showed an increase in frequency of fish consumption as educational level increases among the participants aged ≥65years (Barberger-Gateau *et al.,* 2005). This is because highly educated people may have easy access to healthy dietary information and better understanding of the benefit of fish consumption. However, some studies did not show a significant association of educational level with fish consumption (Trondsen *et al.*, 2004; Verbeke, Vackier, 2005). The discrepancies in the findings of the studies could be due to cultural differences in motivations for fish consumption.

Income was acknowledged in Jensen (2006) as a significant determinant of the purchasing power of consumers' food and services, which affected how food is purchased and consumed. Income was investigated by Can and colleagues (2015) as a significant determinant of fish consumption. Similarly, Barberger-Gateau *et al.* (2005) showed a significantly increase odds of fish consumption among people with increase in income. Another study also suggested that lower income level results into lesser consumption of fish (Verbeke and Vackier, 2005).

Occupational class was recognised as one of the socio-economic factors that can predicts the frequency of fish consumption. This was found in a Taiwan cross-sectional study of 1200 participants aged 14-71 years that reported that odds of fish consumption were reduced among the participants who had blue collar occupations (Li *et al.*, 2001). Similarly, Galobardes, Morabia and Bernstein (2001) in their community-based study of 5696 Swiss adults aged 35-74 years, found a reduced consumption of fish among participants with manual or lower occupational class. People with low occupational class may have low levels of education and income, which appear to reduce the consumption of fish in the population throughout the life course including in older people.

Marital status was acknowledged in previous studies as another factor that influences the consumption of fish. Li *et al.* (2001) found reduced odds of fish consumption among the unmarried participants in a Taiwan cross-sectional study of participants aged 14-71 years. Similarly, Tanskanen *et al.* (2001) observed a reduced intake of fish among the unmarried participants in their cross-sectional study of 3204 Finnish adults aged 25-64 years old. However, Can, Günlü and

Can (2015) cross-sectional study revealed a significantly greater yearly fish intake (1.52 kg) in single compared to married participants. The discrepancies in the findings of these studies could be because those who were never married/divorced had a lower household income, and they may have fewer children at home which influence the demand for fish consumption.

2.9.3.1.2 Situational factors

Situational factors such as living area, fish familiarity, social norms and household and cultural factors were acknowledged by Carlucci *et al.* (2015) to influence the frequency of fish consumption. A Norwegian cross-sectional study of 9407 participants aged 45-69 years acknowledged increased odds of fatty fish consumption among the participants that live in the coastal region when compared to those that live in the inland region (Trondsen *et al.*, 2004). Trondsen *et al.* (2004) and Mryland *et al.* (2000) acknowledged that a significant increase in household size shows a positive increase in the consumption of fish.

2.9.3.1.3 Sensory perception

Sensory characteristics including perceived taste, texture, and smell of fish products are important factors that influence the way fish is consumed (Carlucci *et al.*, 2015). These are essentially used to assess the quality and freshness of fish products. Taste was reported as an important enabling factor that positively influence the consumption of fish as evidenced in a systematic review of 14 studies that reported taste as one of the important influencing factors that affect the consumption of fish and seafood (Christenson *et al.*, 2017). People consider taste of food as very crucial factor as stated in Verbeke (2006) that few people generally consume food with unpleasant taste, since food is consumed based on desire and preference. Taste as an enabler of fish consumption was also acknowledged in the findings of the following previous studies (Bredahl and Grunert, 1997; Olsen, 2004; Verbeke and Vackier, 2005; Rortveit and Olsen, 2009; Birch *et al.*, 2012). Taste could also act as a barrier to people that dislike or consume smaller amount of fish (Birch *et al.,* 2012; Neale *et al.*, 2012).

Previous studies also reported smell as a barrier to fish consumption (McManus *et al.,* 2007; Brunso *et al.,* 2009). A qualitative study of six focus group discussions in two European countries (Spain and Belgium) reported smell during fish preparation as a barrier that influences the consumption of fish (Brunso *et al.,* 2009). This was supported by McManus *et al.* (2007) qualitative study of seven focus group discussions where smell was also highlighted as a barrier to fish consumption.

Presence of bone in fish was also reported as one of the factors that inhibit the frequency of fish consumption. This was shown in a Belgian cross-sectional study that reported bone as a factor that negatively affects the consumption of fish (Verbeke and Vackier, 2005). Other previous studies also reported presence of bone in fish as a barrier that affect the rate of fish consumption (Bredahl and Grunert, 1997; Oslen, 2004; Brunsø *et al.*, 2009; Rortveit and Olsen, 2009; Birch *et al.,* 2012).

2.9.3.1.4 Perceived health beliefs/benefits

Previous studies acknowledged that people widely perceived fish as a healthy food with various nutritional benefits including a high-quality animal protein and a major source of long-chain omega-3 polyunsaturated fatty acids (PUFAs) (Brunsø *et al.,* 2009; Birch *et al.,* 2012; Grieger Miller and Cobiac, 2012; McManus *et al.,* 2012; Neale *et al.,* 2012). This contributed markedly to the rate of fish consumption. Even though most people are aware of the beneficial effect of fish, the knowledge about the constituents that makes fish products important to health is inadequate (Pieniak *et al.,* 2010; Grieger Miller and Cobiac, 2012). Only few people both older and educated are aware of the peculiarity of the nutrients present in fish and their associated health impact on diseases such as heart disease (Brunsø *et al.,* 2009; Grieger, Miller and Cobiac, 2012).

2.9.3.1.5 Convenience perception

Convenience, an ability to maximise and reduce the time and stress encounter during fish preparation is another enabling factor that influences the consumption of fish. Convenience in relation to processed fish products are perceived as a quick and easy meal option that require little amount of time and effort to prepare, while fresh fish products are perceived as difficult meal option because their mode of preparation require huge amount of time and energy. This is evidenced in some previous studies that reported the convenience of having frozen seafood in the freezer as a factor that motivate a quicker preparation and consumption of fish (Jaeger and Meiselman, 2004; Mahon *et al.,* 2006; Brunso *et al.,* 2009; Birch *et al.,* 2012). Convenience was also reported in a qualitative study of 28 occasional seafood consumers in three European countries (Denmark, Iceland and Norway) as part of the factors that positively influence seafood consumption, because participants desire to often consume fish, but are discouraged about the amount of time and effort committed to fish preparation (Altintzoglou *et al.,* 2010). This corroborates with other six focus group discussions conducted in two European countries (Spain and Belgium) where it was reported that participants were concern about the time and effort required to prepare fish, though they desire to regularly consume fish (Brunsø *et al.,* 2009).

2.9.3.1.6 Fish eating habits

According to Carlucci *et al.* (2015) systematic review of 49 studies, few studies have examined the impact of fish-eating habits on fish consumption, despite being a strong predictor of fish consumption. A Norwegian cross-sectional study of 9407 female participants aged 45-69 years suggested that frequent fish consumption habit during childhood can create a constant and established fish consumption habit during old age (Trondsen *et al.*, 2003; Trondsen *et al.*, 2004). A focus group discussion analysis also revealed that frequent fish consumption during childhood influences the rate of fish consumption at old age (Altintzoglou *et al.*, 2010). Likewise, an Australian cross-sectional study of 899 participants aged 18 to over 55 years also reported that regular fish consumption during childhood is likely to create positive, familiarity and favourable attitude towards fish consumption during adulthood (Birch and Lawley, 2014). These findings do not necessarily mean that at old age a person will automatically continue to consume the same amount of fish due to other factors that they might have encountered while growing up, which can negatively influence the frequency of fish consumption (Carlucci *et al.,* 2015).

2.9.3.1.7 Self-efficacy

Self-efficacy refers to the level of knowledge, experience, competence and confidence that an individual requires to successfully carry out a task of fish preparation. This level of competence is essential so that adequate and thorough quality assessment is carried out while purchasing the fish products and during fish preparation. Lack of this self-efficacy could negatively affect the frequency of fish consumption. Low self-efficacy was reported by previous qualitative studies as a very crucial factor that can negatively affect the consumption of fish (Altintzoglou *et al.*, 2010; Birch *et al.,* 2012; Neale *et al.,* 2012). Previous cross-sectional studies also acknowledged that the frequency of fish consumption is positively influenced by the preparation and selection of fish products with high level of skills and self-confidence (Birch and Lawley, 2012; Birch and Lawley, 2014).

2.9.3.1.8 Availability

Availability is considered in previous studies as a strong predictor of fish consumption, because lack of availability of variety of fish to choose and purchase could negatively affect the frequency of fish consumption (Carlucci *et al.,* 2015). Fish products are presently not only available in the coastal region but also available to those living far from the coast, all thanks to the current production, mode of transportation and preservation technique that made fish products accessible to the non-coastal areas. A cross-sectional study of 823 Australian lower fresh/finfish/seafood consumers reported availability as one of the barriers that negatively influence the consumption of fresh, frozen fish and seafood (Grieger, Miller and Cobiac, 2012). In a Norwegian women study of 9407 participants aged 45-69 years, lack of availability of fresh fish was also reported as a barrier of fish consumption (Trondsen *et al.,* 2003). Similarly, Birch *et al.* (2012) mixed methods research reported availability as one of the barriers that affect the purchase and proper consumption of fish.

2.9.3.1.9 Price perception

Different types of fish products are sold at varying market prices with a wide range of price, where some might be quite expensive and others very cheap. Despite the wide range of prices, fish products are generally considered more expensive when compared to other sources of protein e.g. meat, while some people consider fish as less filling (Carlucci *et al.,* 2015). Price or price perception was acknowledged in previous studies as an important factor that negatively influence the consumption of fish (Kreider *et al.,* 1993; Trondsen *et al.,* 2003; Olsen, 2004; Verbeke and Vackier, 2005; McManus *et al.,* 2007; Brunso *et al.,* 2009; Neale *et al.,* 2012; Thong and Sagaard, 2017; Wenaty *et al.,* 2018). Birch *et al.* (2012) Australian mixed method research of 60 (10 focus groups) and 1815 participants aged 18 to over 55 years reported cost/price as the most significant barrier that affected the purchase of both fresh fish and seafood with shorter shell life due to their expensive nature. In three focus group discussions study of three European countries (Denmark, Iceland, Norway), fish was perceived as very expensive by the participants, which affected the way fish was purchased and consumed (Altintzoglou *et al.,* 2010).

Other existing theoretical frameworks that have been previously applied to describe different but interrelated factors influencing the consumption of fish include the Theory of Planned Behaviour (TPB) (Ajzen, 1991; Scholderer and Grunert, 2001; Verbeke and Vackier, 2005; Brunsø *et al.*, 2009; Birch and Lawley, 2010; Higuchi, Davalos and Hernani-Merino, 2017; Arsil and Yanto, 2019), the Theory of Reasoned Action (TRA) and the attitude strength theory (Olsen, 2001).

The TRA is a model that is meant to predict human behaviour and makes use of individual beliefs and attitude about the intended behaviour (Fishbein, and Ajzen, 1975; Ajzen and Fishbein, 1980). However, having an intention to execute a certain health related behaviour does not necessarily predict the performance of the behaviour (Baranowski, 1990). This led to the extension of the TRA model in the TPB by the addition of another variable called the perceived behavioural control to explain the gap between intention and behaviour (Ajzen, 1991; Glanz, Rimer, and Viswanath, 2015).

Oslen (2001) integrated two extensional variables with the TRA that comprises of attitude towards behaviour and social norms to measure the involvement in fish product consumption. These two new variables including negative feelings and moral obligation are antecedent of involvement that was derived from the attitude strength theory, a theory that explains the structure and relationship of attitude and attitudinal behaviour. However, this model lacks all other necessary variables required to drive and establish the aim of this study.

Unlike other conceptual framework, the theory of planned behaviour derived from the TRA and including attitude towards behaviour, subjective norms and perceived behavioural control (PBC) has been extensively used in previous studies to predict the intention to consume fish (Ajzen, 1991), but lack variables like knowledge, self-efficacy, previous experience and habits on attitude and fish consumption behaviour. Therefore, an integrative framework was proposed by Arsil and Yanto (2019) to accommodate these deficiencies by incorporating together both Zepeda and Deal (2009) Alphabet theory and TPB, but still the variables were not well elaborated, thus necessitated the adoption of Carlucci *et al.* (2015) conceptual framework in this study, which is explicit, robust and well organised and aligned with the variables assessed in this thesis.

Carlucci *et al.* (2015) incorporated health belief as part of the factors that can influence the consumption of fish, therefore directly accommodated the Rosenstock *et al.* (1988) Health Belief Model (HBM) which provided a meticulous approach to accept and organise personal beliefs that are significant to health behaviour. HBM is a "value expectancy model" that suggest how peoples' behaviour is determined through appreciation of a certain goal and taking positive action to achieve that goal (Poss, 2001). Janz and Becker (1984) declared that HBM was developed basically to visualise precautionary health behaviours and its therapeutic response to chronic diseases. According to Gillum (1991), HBM has been used to predict protective health behaviour such as the consumption of fish. This model also highlighted that people engage in healthy behavioural change based on their feeling about their susceptibility to a disease (dementia), and their awareness about the consequences and the believe that a behavioural change (fish consumption) can prevent or reduce the risk of the disease (dementia) (Glanz, Rimer, and Viswanath, 2015). Abraham and Sheeran (2005) also emphasised that HBM model explores how beliefs influence behavioural change. Therefore, this model highlighted that people must perceived certain beliefs to achieve a behavioural change, since behaviour was postulated as a function of peoples' knowledge, attitude and socio-demographic characteristics (Iriyana, 2007). These include perceived susceptibility to the illness and its predisposing factors, the anticipated seriousness of the disease, the benefit of implementing the behaviour that is self protection and safety as well as having the competence to overcome the barriers to its implementation. When these health beliefs are understood from the nutrition and health education perspectives (i.e., the importance of fish consumption) or perceived symptoms standpoint, this could motivate healthy behavioural change. The “cues to action”, a part of this model shows the likelihood that an individual will perform a self-protective action if well informed about the possible health problem (dementia). This could be through witnessing the manifestation of a disease in a close family member or friends, through media campaign, peoples’ advice, counselling from health practitioner or via a newspaper article (Rosenstock *et al.,* 1988). However, this model was criticised for primarily focusing on the health problem rather than on the behaviour of people with the disease (Humphris and Ling, 2000). They also highlighted that behaviour is formulated by external forces and individual factors and not only through economic assessment of the disease (Humphris and Ling, 2000). The HBM is a good framework that appreciates the fundamentals of human actions, based on the notion that being susceptible to a disease arouses human behaviour (Rosenstock *et al.,* 1988). This makes the model quite suitable for this study.

Figure 2.2: The Integrated Framework of Carlucci et al. (2015) and Health Belief Model

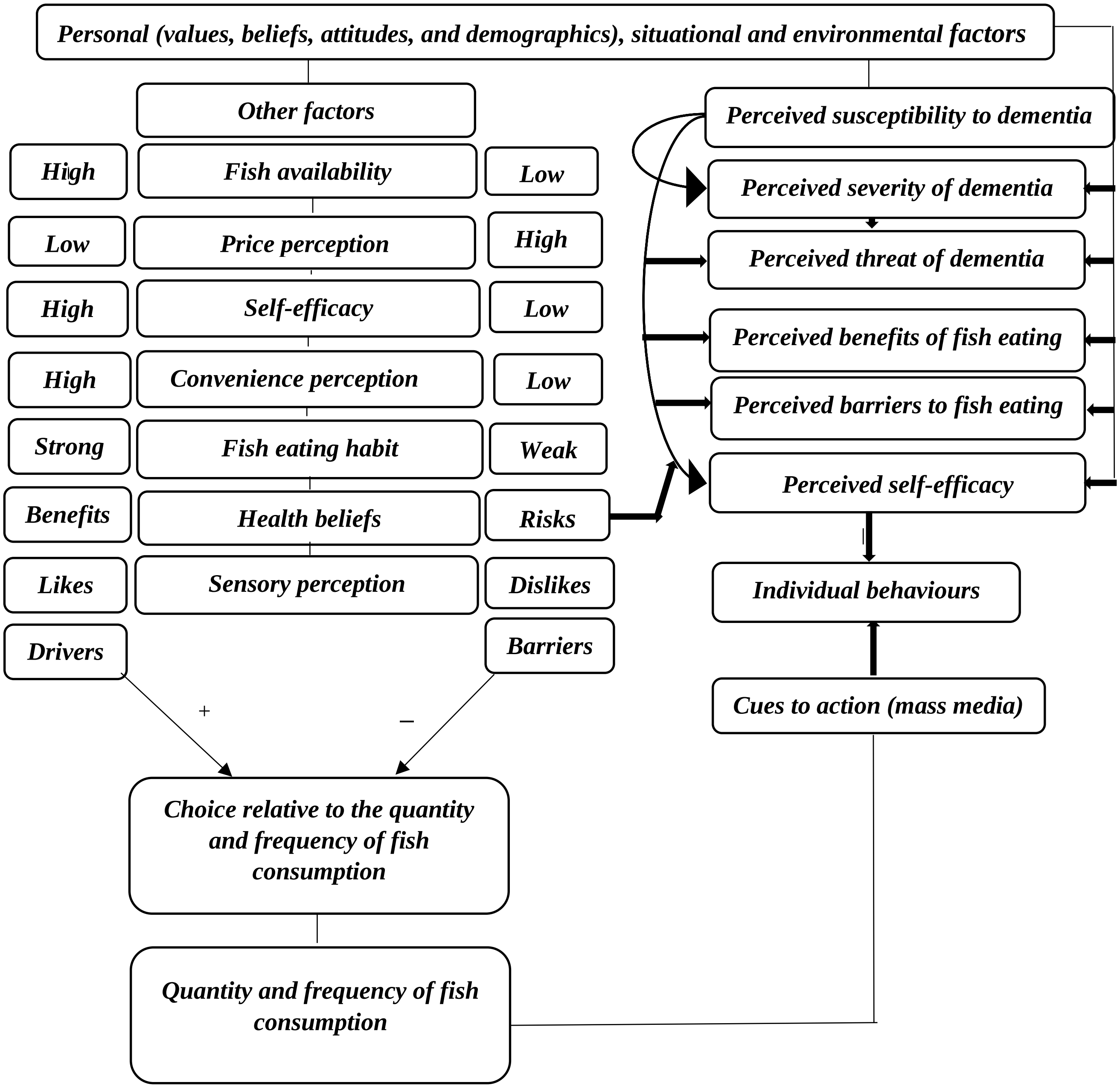


Figure 2.2: The Integrated Framework of Carlucci *et al.* (2015) and Health Belief Model.

2.10 Rationale for the study

There are few studies which have been carried out to examine the association between fish consumption and the risk of dementia, and their findings are inconsistent. These studies are predominantly from the HIC countries, while data from low- and middle-income countries (LMIC) is limited. Although some studies have reported the factors that influence the consumption of fish among extensive age range or assessed only female participants, few studies have specifically examined factors that influence the consumption of fish in older people, despite the world population aging and having the higher risk of developing cardiovascular and neurodegenerative disorders. Therefore, it is paramount to explore the impact of fish consumption on the risk of dementia and the determinants that can affect its rate of consumption among older people.

Moreover, previous studies on fish consumption and dementia are predominantly of quantitative design (Barberger-Gateau *et al.,* 2007; Devore *et al.,* 2009; Lopez *et al.,* 2011). Since this study design does not reflect people's views and perception, it is expected that through discussing with people, this study will better understand people's views on the consumption of fish in relation to the risk of dementia and the determinants that can affect its consumption. The findings of the proposed qualitative research should complement the quantitative data about the reasons why people consume (or don't consume) fish and to know whether they are aware of its beneficial impact on health especially in reducing the risk of dementia. This will thus contribute to a currently limited evidence base on people's perception of the health benefit associated with fish consumption.

2.10.1 Aim and objectives

2.10.2 Aim of the study

The main aim of this study is to conduct a systematic literature review and examine the determinants and impacts of fish consumption on the incidence and mortality of dementia in older people using a convergent parallel database mixed methodological approach.

2.10.3 Objectives of the study

The objectives of this study are:

- To examine the determinants of fish consumption in older people.
- To conduct an updated systematic review and meta-analysis on the impact of fish consumption on the risk of dementia.
- To assess the association of fish consumption with incidence of dementia in older people.
- To examine the impacts of fish consumption on all-cause mortality in older people with and without dementia.
- To explore people's perceptions and attitudes toward fish consumption and the risk of dementia and the determining factors that can affect the consumption of fish by conducting focus group discussions.

2.11 Summary

Although most of the published studies reported an inverse association of fish consumption with the risk of dementia, it is apparent that the results are not consistent, suggesting further research on the impacts of fish consumption on the risk and outcome of dementia. This current dissertation investigated a modifiable dietary factor: fish consumption that could be a predictor of the risk and outcome of dementia. This was achieved through six independent studies that attempted to build on the previous literature and assist in understanding whether a dietary factor - fish consumption can be instituted as an intervention strategy to delay or reduce the risk of dementia. This study is the first to apply a convergent parallel database mixed methodological approach that involve incorporating both the qualitative and quantitative research design to investigate the impacts of fish consumption on the incidence and mortality of dementia in older people.

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter outlines the methodology and methods employed to investigate the impacts of fish consumption on the incidence and outcome of dementia and examine factors influencing the consumption of fish in older people. It provides the background to the mixed method pragmatic approach and demonstrates how it informs the study by discussing its importance as a theoretical framework. It also explains all the other existing philosophical paradigms. This chapter demonstrates the selection and description of a mixed methodological approach. Its importance is elucidated through highlighting its validity and usefulness to this study method of data collection. This chapter also describes the study design, participants, data collection including interview materials and instruments, data analysis methods, ethical considerations and trustworthiness of this study.

Research methodology is a scientific and organised way of conducting research (Rajasekar, Philominathan and Chinnathambi, 2006; Chinnathambi, Rajasekar and Philominathan, 2013). It is a procedure that involves the description, prediction and explanation of the theoretical concept of research, which systematically proffers solution to a specific problem (Chinnathambi, Rajasekar and Philominathan, 2013). It is also the science of choosing a specific method to conduct research and how this method is connected to the outcome of the research (Crotty, 2009); that is, the general approach to research that is connected to its theoretical framework (Mackenzie and Knipe, 2006). Research methods are the various procedures involving structures and techniques including data collection and analysis that is employed by a researcher to conduct a research study (Mackenzie and Knipe, 2006; Rajasekar, Philominathan and Chinnathambi, 2006; Onwuegbuzie and Frels, 2016). This thesis is positioned within the tradition of mixed methods, which involve the combination of both the quantitative and qualitative methodological approaches. Using such a research methodological approach (mixed methods) to conduct research that is predominantly of quantitative design could complement and provide a comprehensive investigation and enrich the findings of a study. This will thereby contribute to a currently limited evidence base associated with using only one research approach (Johnson and Onwuegbuzie, 2004). This tradition nullifies the declarations that different types of data and their analysis techniques are incompatible, and therefore must not be adopted together in the same study (Howe, 1988). This research contests this by confirming that ensuring a careful combination of different types of data and analysis techniques can disclose the different magnitudes of a problem and its solution, thus increasing its depth of knowledge and understanding (Creswell, 2009). Therefore, mixed method research attracts the strengths and reduces the weaknesses of both the quantitative and qualitative research methods, because both research approaches are valuable and significant (Johnson and Turner, 2003; Johnson and Onwuegbuzie, 2004; Kelle, 2006; Tariq and Woodman, 2010; Yardley and Bishop, 2015).

3.2 Research Paradigms

Research is a rational and systematic exploration of valuable information which involves the collection, analysis and interpretation of data to describe and properly understand its phenomena (Mertens, 2005; Mackenzie and Knipe, 2006; Rajasekar, Philominathan and Chinnathambi, 2006). Mertens (2005) states that the specific nature of research definition is inclined towards theoretical frameworks, which are referred to as “research paradigms”. Theoretical framework is therefore, defined as a structure that demonstrates the processes that help to understand a research phenomenon, thereby highlighting the researcher’s assumptions and philosophical views in solving a research problem (Polit and Beck, 2010). This theoretical framework influences the knowledge and interpretation of a study, and guides the principle that drives the intention, motivation and expectation of a research study (Mackenzie and Knipe, 2006). This theoretical framework is a theory that is usually applied to generate the associations between concepts that explain a phenomenon (Mertens, 2005). Choosing a research paradigm is paramount in the early stages of a research study to lay the foundation for selecting the research design, methodology and methods to conduct a research study. Paradigm is therefore defined as a philosophical intention or determination to conduct a research study (Cohen and mansion, 1994). It involves the collection of reasonably related assumptions and ideas or suggestions required to conduct a research (Mackenzie and Knipe, 2006). Creswell (2003) explains this theoretical framework as a "knowledge claim" involving epistemology or the ontology viewpoint, or basically research methodologies (Neuman, 2000).

The association between the philosophy of research and methodology lies in the fact that methodology must be guided by a certain philosophical principle. This research paradigm comprises three fundamental components that include methodology, study validation and knowledge belief (Mac Naughton, Rolfe and Siraj-Blatchford, 2001). These theoretical paradigms include positivism, interpretivism/constructivism and pragmatism. These paradigms are based on different ontology and epistemology stances.

Ontology is people's understanding of the nature of social reality and existence, which means the study of the existence of something (Grix, 2002; Mark, 2010). Epistemology refers to the way the knowledge of social reality is acquired (Grix, 2002; Mark, 2010). That is the science and philosophy of knowledge (Hay, 2006), rooted in a theoretical perspective, hence the methodology (i.e. the specific ways to know that reality) (Guba, 1990; Crotty, 1998). Epistemology involves the process of acquiring knowledge through which theories and new models are discovered (Grix, 2002). Therefore, good research is informed by the ontological and the epistemological assumptions, which thereby informs the methodology used in executing the research (Mark, 2010).

3.2.1 Positivism

Positivism is a scientific method of research which expresses the empiricist philosophy that causes possibly determine outcomes (Sale *et al.*, 2002; Creswell, 2003; Mertens, 2005). This philosophical paradigm is of the assumption that the social and the natural world can be studied using a similar approach, thereby, providing explanations of a causal nature (Mertens, 2005). Positivists engage in observing and measuring concepts with the intention of evaluating and predicting their outcomes, thus achieving an objective reality independent of being influenced by the study participants (O'Leary, 2004; Mark, 2010). Positivists use a deductive research approach (top-down approach), which is an objective way of solving research problems (Feilzer, 2010; Mark, 2010). The positivist paradigm mostly aligns with the quantitative methodological approach, which involves the collection of factual data to explore the associations between these facts and how they agree with the findings of other existing research (Mackenzie and Knipe, 2006).

3.2.2 Interpretivism

Interpretivism, also known as constructivism or subjectivism, is an approach to research that involves the intention to understand peoples' life experiences (Cohen and Manion, 1994; Mark, 2010). It involves the ability to be able to socially construct reality (Mertens, 2005; Mark, 2010). Interpretivists rely on the participants' perception of the topic being studied, since people's experiences and the way they perceive things differs from one another, which is mainly due to socialisation (people's background) (Creswell, 2003). Interpretivists use an inductive approach (bottom-up approach) to generate or develop a theory during a research process (Creswell, 2003). The interpretivists' paradigm, although applicable to quantitative approach, mostly aligns with the qualitative methodological approach or the mixed methodological approach that involves the combination of both the qualitative and quantitative methods to complement and support their findings (Mackenzie and Knipe, 2006).

3.2.3 Pragmatism

Pragmatism is not dedicated to a certain philosophical paradigm (Mackenzie and Knipe, 2006). Its emphasises the 'what' and 'how' of a research problem (Creswell, 2003, p.11). Pragmatists believe that more than one scientific method could be used to conduct a research study (Mertens, 2005). This means more than one philosophical perspective is required to entirely explain a research question to achieve a complete reality (Creswell, 2003; Denscombe, 2008). Therefore, pragmatism is a paradigm that provides the fundamental theoretical framework for the mixed-methods approach, where two traditional perspectives (positivist and interpretivist) are combined to achieve a better understanding (Tashakkori and Teddlie, 2003; Somekh and Lewin, 2005). Pragmatism involves the combination of different worldviews and assumptions that incorporate different data collection and analysis techniques (Creswell, 2003). This philosophical stance can be obtained out of action, circumstances and consequences (Tashakkori and Teddlie, 2010). Unlike the other traditional paradigms, pragmatism is more concerned about the research problems and questions instead of the methods, thus concentrating on the outcome and applications of research (Creswell and Plano Clark, 2007; Feilzer, 2010). Therefore, pragmatics utilises both the qualitative and quantitative mode of data collection to achieve its research objectives (Creswell, 2007; Feilzer, 2010). Even though some methodological purists claim that it is inappropriate to combine both the positivist and the interpretivist viewpoints owing to their epistemological and ontological incompatibilities (Johnson and Onwuegbuzie, 2004); various research studies that adopted the pragmatic perspective have been conducted. In these cases, the mixed methodology approach does complement the findings of the research. Mixed methods design can therefore strengthen the interpretations of research findings (Tashakkori and Teddlie, 2003). Pragmatic researchers have the freedom to select any procedures and methods that suit their research purposes due to the flexibility in their philosophical standpoint. This flexibility is popularly perceived to be beneficial by some researchers, while others believe it is problematic due to the absence of established guidelines and the tendency to be subjective, thus choosing "what works" to solve a research problem (Evans, Coon and Ume, 2011; Hesse-Biber, 2015). The subjectivity of this pragmatic theoretical framework that involves using all the available research methods sometimes allows the trustworthiness of research to be queried (Smith *et al.*, 2012). These limitations could be minimised by being critically reflective and clearly stating the context in which the research aims, and questions were formulated, which is in line with Hesse-Biber's (2015) recommendation. This is necessary to provide justification for the chosen methodology. This trustworthiness in research issue will be thoroughly discussed later in this chapter.

This present research has adopted the pragmatic stances, where data are collected, analysed, combined and interpreted using the quantitative and qualitative research approaches (Feilzer, 2010). This pragmatic framework remains the most suitable theoretical framework for this study since the other available frameworks are not enough to answer the research questions. Pragmatism is perceived as a concept that demystifies both 'truth' and 'reality', but emphasises everything that works regarding the research questions (Tashakkori and Teddlie, 2003).

3.3 Mixed Methods Research

Mixed methodology is a research paradigm that involve the use of both the qualitative and quantitative research methods (combination of both numbers and words) to answer complex research questions (Creswell and Clark, 2007; Lingard, Albert and Levinson, 2008). This is achieved through using the valuable features of each of these two research methods to broaden the scope and understanding of a research problem (Mackenzie and Knipe, 2006; Creswell, 2009). Mixed methodology is a research approach that uses several perspectives and standpoints to achieve a research goal (Johnson and Onwuegbuzie, 2007). Mixed methods use a pragmatic "philosophical assumption" to drive its process of data collection and analysis, which involve the combination of both the qualitative and quantitative methods in a study (Creswell and Clark 2007). This pragmatic philosophical assumption involves using the best method to achieve a desired result. Historically, this approach has been used in the social and behavioural or human sciences (Creswell, 2009). It started with the belief that the combination of quantitative and qualitative viewpoints and methods were useful to address a research question (Johnson *et al.,* 2007). Mixed methodology - a paradigm that is justified by the pragmatic philosophy was used to achieve the goals of this study. This method provides robust inferences and opportunities to demonstrate the variety of different views and ideas (Tashakkori and Teddlie, 2003). This research approach provides a better opportunity to solve a problem that either the quantitative or qualitative design approach can singly achieve (Tashakkori and Teddlie, 2003; Creswell and Plano Clark, 2007). Mixed methodology is a research approach that strengthens and reduces the weaknesses of both the quantitative and qualitative research (Johnson and Onwuegbuzie, 2004; Kelle, 2006), thus appropriate for this current study to achieve a better understanding and solid conclusion as well as to ensure a rigorous approach is used in solving the research problem. This research approach provides researchers the opportunity to use different data collection tools and technique to solve the research questions. Mixed methods pluralistic approach to research provides answers to questions that could be difficult to answer using a singular approach, thus encourages research collaboration. This exposes the research to different ideas, worldviews and paradigms that signifies an applied research method. The concept of mixed methods involves solving problem by applying both words and numbers to achieve a desired result. Since this study adopted a pragmatic approach to research; no specific method was chosen to answer the research questions. Both the quantitative and qualitative research methods were used to complement each other. This means, where one approach has difficulties in comprehensively answering the research questions, an additional approach was applied to gain proper understanding of the research under investigation.

3.3.1 Strengths and Limitation of Mixed Methods

Using a mixed method approach in any study has its strengths and limitations. The strengths include giving the researcher the opportunity to properly criticise all other types of research, reducing the wastage of valuable information, strengthening the result of a research using various methods, and positively impacting on the decision of policy maker due to the use of both figures and words (Gorard, 2004). This study used a method that incorporated different methodological approaches to balance the intrinsic biases in each of the singular approach, which could create an avenue to achieve comprehensive and diverse information from a phenomenon. Mixed methods create a more differing result, which increases the robustness and strengthens the interpretations of a result. Additionally, it provides the opportunity to see the comprehensive and clear picture of the study under investigation and a mutual validation of results (Kelle, 2006). Despite the various advantages of a mixed methods approach, it has limitations. These include the use of various expertises, time consuming nature of the data collection and analysis, resources and the synthesis of lots of information (Creswell, 2017). Regardless of these limitations, the researcher chose the mixed method approach as the most suitable for this study, because of its level of strength.

3.4 Quantitative and Qualitative Research Design

Quantitative and qualitative methodology are two distinct research approaches that offer useful evidence-based in public health research (Johnson and Onwuegbuzie, 2004). Both methods are often used in two different ways. They are usually either referred to as research paradigm or research methods (Mackenzie and Knipe, 2006). These two research methods refer to the peculiarities concerning the "nature of knowledge" which connotes how the world is perceived and the importance of research (McMillan and Schumacher, 2006). In another perspective, quantitative and qualitative methods of research refer to the process of data collection, analysis, and interpretation of the data (McMillan and Schumacher, 2006). O'Leary (2004) refers to qualitative and quantitative research as type of data and the method of analysis.

3.4.1 Quantitative Research

Quantitative research method involves the use of numbers and things that are measurable to systematically investigate a phenomenon and their associations with other variables to ascertain and predict the phenomenon (O'Leary, 2004; Rajasekar, Philominathan and Chinnathambi, 2006). Creswell (1994) defined quantitative research as a method that involves the explanation of phenomenon through collection of numerical data and analysis using different statistical method. Quantitative research stresses the importance of measurement and analysis of data to derive causal associations between variables (Denzin and Lincoln, 1998). This method of research starts with the collection of data based on certain theory, followed by the analysis of the data involving the use of descriptive and inferential statistics (Rajasekar, Philominathan and Chinnathambi, 2006). Quantitative research gives a researcher the opportunity to get acquainted with the research problem under investigation through hypotheses generation (Golafshani, 2003). This research method allows the researcher to use standardised measures to ensure that various viewpoints of different people fit into a restricted number of response categories that are predetermined (Patton, 2002). Therefore, quantitative research involves the construction of a suitable instrument that is administered using a standardised method to collect information from participants during a survey (Golafshani, 2003). Survey is a kind of research that involves the use of large or small number of people that are carefully sampled from a specific population through randomisation to understand and learn about their behaviour (Sukamolson, 2007). In this kind of research, participants are asked series of questions using a specified questionnaire, and their responses are later summarised using various statistical method of analysis (Sukamolson, 2007). Using quantitative research in a study has its strengths and limitations. The strengths include using different sampling technique for proper estimation of the population at large, allowing results to be statistically analysed and summarised using various group comparison, as well as having a standardised and definitive precision (Sukamolson, 2007). Its limitation lies in its inability to generate in-depth knowledge about a particular topic under investigation (Babbie, 1990; Bryman, 2008).

3.4.2 Qualitative Research

Qualitative research involves the recognition of how knowledge is produced through active participation of the researcher in a study (Henwood, 2014). This involves thoroughly listening, recording and contextualizing people’s action, thought and live experiences (Henwood, 2014). Qualitative research is a process of research that does not require any statistical procedure or form of quantification to arrive at a desirable result, since they utilise “non-numerical data” (Strauss and Corbin, 1990; Sukamolson, 2007). This research method is less structured compared to the quantitative methods and are exploratory in nature (Jarratt, 1996). Qualitative research uses an inductive analytical approach to explore and understand the participants’ perspective about a research problem through identification of themes from the answers provided to the research questions (Creswell, 2012). Golafshani (2003) reported that qualitative research uses a naturalistic approach to research to try to understand and find answer to a problem in a ‘real world’ setting. This research approach achieves their research outcome from a real-world situation by gradually unfolding a natural phenomenon (Patton, 2002; Camic, Yardley and Rhodes, 2003; Robson, 2011). Qualitative researcher uses pictures, words, and images to find solution to research problems through thematic exploration (O'Leary, 2004). Although qualitative research provides different methods of exploring questions about peoples’ social and psychological life (Camic, Yardley, and Rhodes, 2003; Henwood, 2014), it has some limitations. These include the use of small sample size, which is certainly not representative of a wider population, thereby limiting the generalisability of the findings (Atieno, 2009). Also, the lack of rigour in the findings makes it difficult to notice if the results were influenced by the idea of the researcher. In qualitative research, no effort is made to manipulate the phenomenon under investigation, but rather expose and report it naturally using the participants own words. This research approach is not really concerned about the causal association, prediction and generalisability of findings, but instead it is concerned about the understanding and illumination of similar circumstances (Hoepfl, 1997). Therefore, using a qualitative method in this study, the researcher hopes that an in-depth knowledge and a true representation about the views and perceptions of older people on the impact of fish consumption on dementia and other health outcomes will be achieved.

Nevertheless, for any research work, there is need to provide answers to several research questions by using a qualitative or quantitative research approaches considering the type of research questions. Therefore, a survey using questionnaires as a form of data collection can be used to identify the level of a research problem. Nonetheless, since a survey is generally criticised for not producing a detailed understanding of a specific research problem (Babbie, 1990; Bryman, 2008), a focus group discussion can be used to further describe and explore the views and perception of older people.

In this research, both quantitative and qualitative data were collected for analysis. Such mixed approach methods for data collection complement each other, making better understanding of the global overview of the association between fish consumption and dementia risk and the determinants that affect its consumption among older people.

3.5 Research Design

The quantitative part of this research was longitudinal in design (i.e. prospective cohort in nature) and is based on an existing cohort study dataset in China. A cohort study measures the occurrence of a disease and its temporal relationship with an exposure, thus ascertaining a causal association (Song and Chung, 2010). A cohort study involves following up a certain group of people over a period of time to determine the incidence of a specific disease or death from this disease or all-cause mortality (Morabia, 2004). In a cohort study, multiple outcomes can concurrently be investigated, and it is good for studying rare exposure (Hulley *et al.*, 2001; Elwood, 2007; Owen *et al.*, 2018). Its limitations lie in the use of large sample size, long follow up period, its expensive nature, its susceptibility to selection bias, potential and residual confounders, difficulty in preserving the follow-up participants and loss to follow-up or withdrawals (Hulley *et al.*, 2001; Elwood, 2007; Caruana *et al.*, 2015). Regardless of these limitations, a cohort study has carefully been considered to be more suitable for this study, instead of the other types of observational studies, because the benefits outweigh the weaknesses, and this research is interested in using an existing secondary dataset that was collected over a long period of time to determine the incidence of a specific disease and death from this disease. However, a preliminary cross-sectional study was conducted to assess one of the objectives of this study: the association of fish consumption and the risk of dementia to accommodate the large sample size and interestingly the findings were similar to that of the cohort study design. But the limitations of a cross-sectional study design that include inability to ascertain a causal relationship and its limited generalisability (Ronald, 2006; Sedgwick, 2014; Owen *et al.,* 2018), thereby necessitated the use of cohort study design for this study.

3.5.1 The Convergent Mixed Method Design by Parallel Databases

Additionally, the convergent mixed method design (sometimes known as concurrent design) was used in this study during the process of data collection. This convergent form of mixed method occurs when two different, but complementary data (quantitative and qualitative) are collected and analysed independently, and their results merged and compared together during interpretation to ascertain whether they support or contradict each other (Creswell, 2011; Subedi, 2016; Creswell and Clark, 2017). This kind of design shows that one dataset is not enough to answer different research questions, thus requiring different data types. Researchers incorporate this design when a qualitative or quantitative data is required to answer a research question in a study that is largely quantitative or qualitative in design, thereby mixing these different datasets at the point of interface, i.e., the interpretation stage. There are different variants that can be used to implement a convergent mixed method research (Creswell and Clark, 2017). Of all these variants, the "parallel databases variant design" was found to be the most appropriate for this current research (Creswell and Clark, 2017). Figure 3.1 shows a pictorial illustration of this variant. This convergent parallel-databases variant involves the collection and analysis of two parallel datasets independently and then merged at the point of interface i.e., the interpretation phase. These two data types (i.e., both quantitative and qualitative data) are used to explore same phenomenon and their results are later combined and compared at the discussion stage, thus converging the two data sources (Subedi, 2016; Creswell and Clark, 2017).

This variant allows more results to emerge following the contribution of the two datasets. Although these two methods of data collection and analysis are independent, they both play a complementary role for each other through creation of an in-depth understanding of the research questions (Creswell and Clark, 2017). Because integration is very crucial in mixed methods research, I have integrated (merged) the quantitative part of this research with the qualitative part in the discussion. This would help to achieve a thorough combination or comparison and understanding of the research questions (Fetters, Curry and Creswell, 2013). The quantitative phase of this research aimed to provide a numeric data that is generalisable to the entire population, while the qualitative phase aimed at using words to describe and understand the perception and views of older people about the research topic under investigation. This allows the researcher to use a more inductive approach to research through incorporation of a semi-structured discussion guide and analysed using thematic analysis.

In addition, the chosen variant for the implementation of this mixed-method research was guided by three crucial factors highlighted by Creswell (2009). These include timing, weighting, and mixing decision.

Timing, one of the factors considered in mixed method research involves two different ways of collecting data (Creswell, 2009). This could be sequentially or concurrently (Creswell, 2009; Halcomb and Hickman, 2015). In this research, the concurrent timing was adopted, where quantitative and qualitative data were collected in parallel, with both process of data collection done concurrently. This is because the qualitative data was collected to complement the quantitative findings of this research.

Weighting, a second factor considered entails the degree of priority assigned to the two data collection phases in a mixed method research (Creswell, 2009; Halcomb and Hickman, 2015). The weighting could be equal or unequal (i.e. putting emphasis on one method than the other). Equal weighting was chosen in this research as equal emphasis was given to both the quantitative and the qualitative methods, therefore playing a complementary role to each other.

Mixing, another crucial factor in implementing a mixed method research was emphasised by Creswell (2009) to occur at different stages. This could occur at the research question, philosophy, data collection, data analysis and the interpretation stage. In this research, both the quantitative and qualitative data were mixed at the overall interpretation stage, thereby complementing each other. Creswell and Plano Clark (2007) highlighted three ways of combining both the quantitative and qualitative data types. This includes embedded, connected and integrated (merged). Integration type of mixing was chosen in this study. This involves "integrating two parallel databases i.e both quantitative and qualitative data together for comparison to know where they converge or diverge (Fetters, Curry and Creswell, 2013). In this study, both the quantitative and qualitative data are collected and analysed separately and mixed at the interpretation phase (discussion), with both the quantitative and the qualitative data complementing each other through provision of additional information.

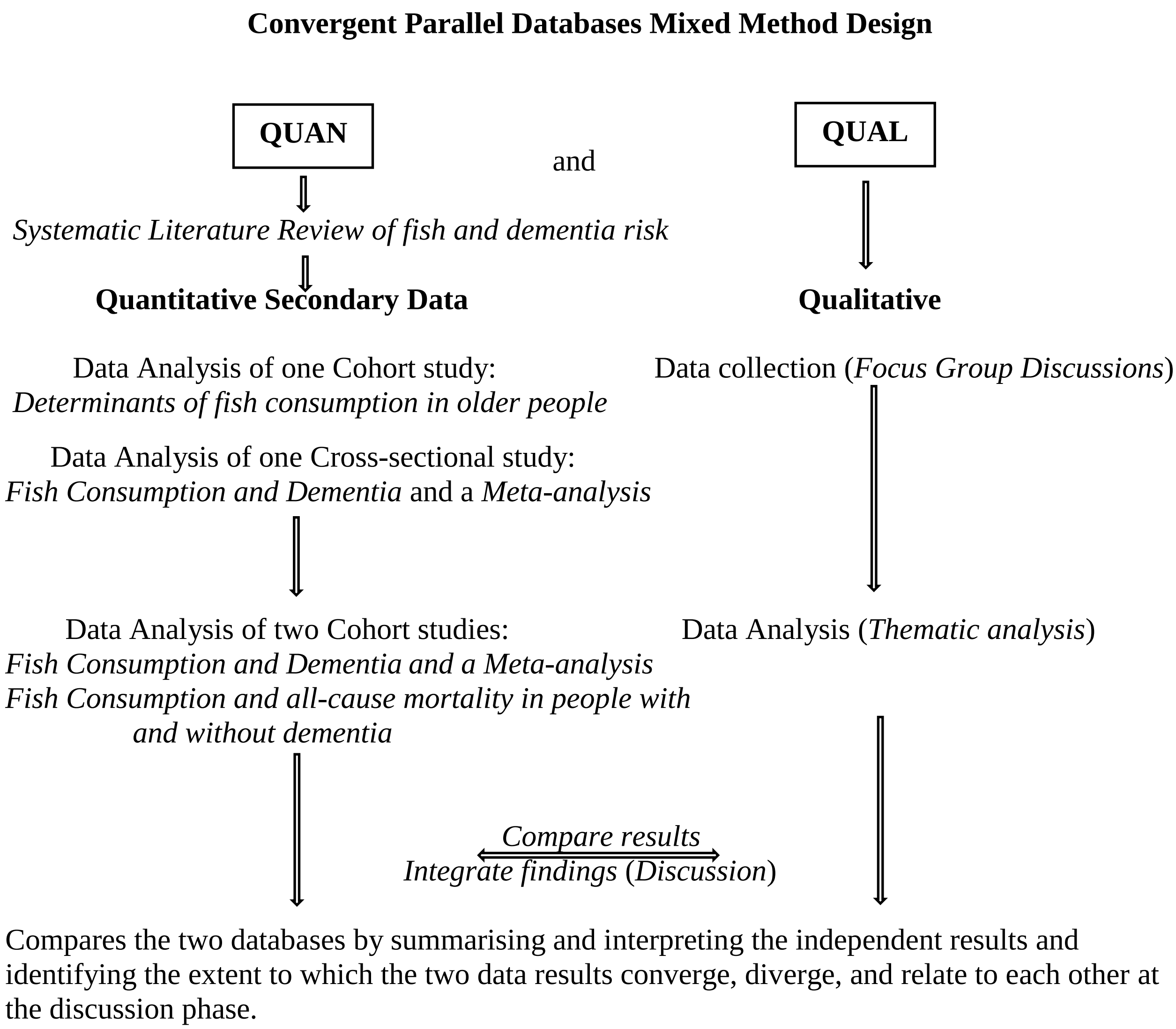


Figure 3.1: Showing the Pictorial illustration of the Convergent Parallel Database Variant Mixed Method Design Applied in this Research Source: Adopted from Creswell and Clark (2017).

3.5.2 Methodological Framework

A methodological framework that visually shows all the entire research process and the components of the convergent parallel databases mixed methodological approach employed in this research is illustrated in the diagram below (see Fig 3.2).

Methodological Framework: Convergent Parallel Database Mixed Method Design

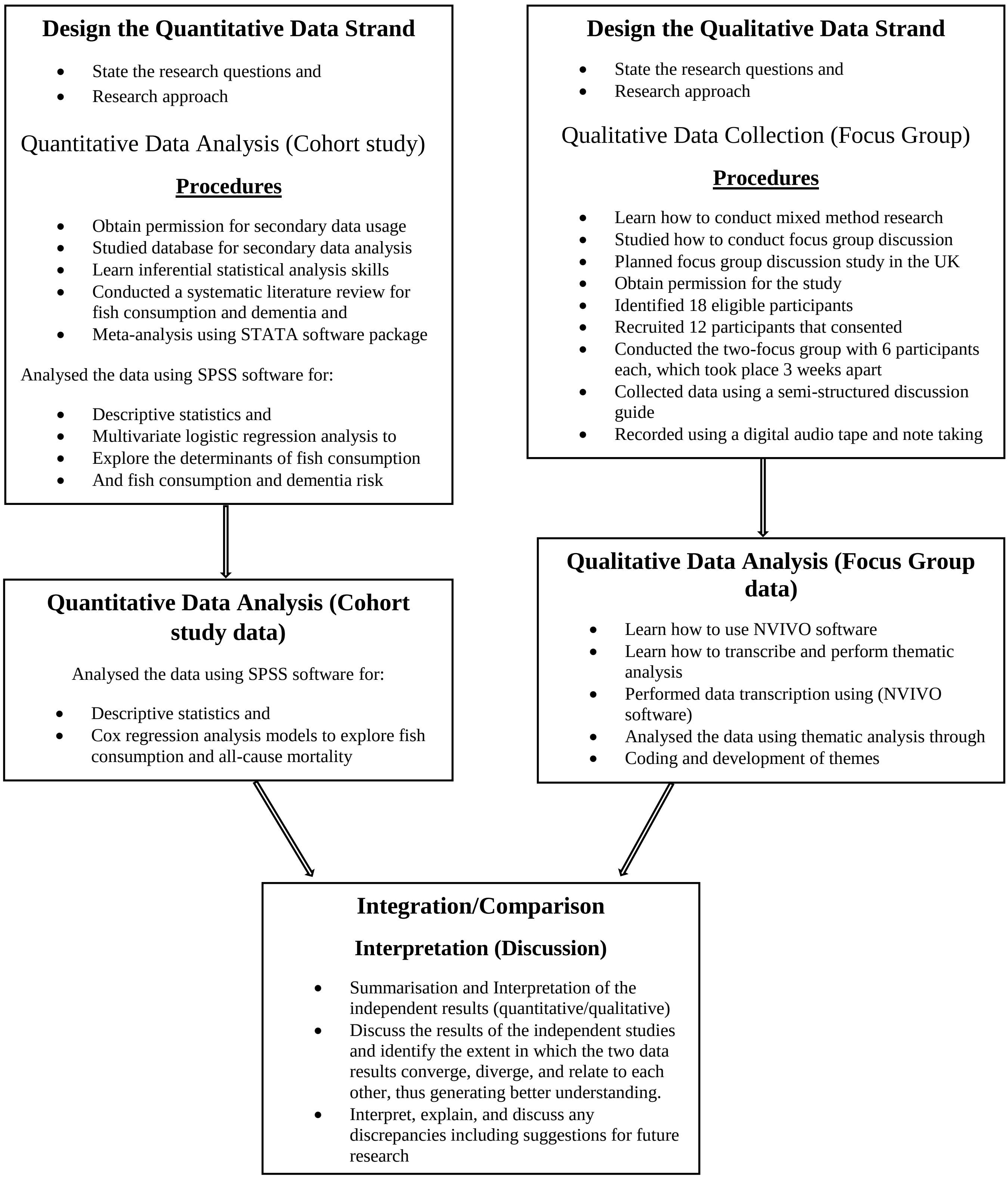


Figure 3.2: Showing the Pictorial illustration of the Methodological Framework for the Chosen Mixed Method Design Source: Adopted from Creswell and Clark (2017).

3.6 Research Methods

Research methods are the various procedures involving structures and techniques including data collection and analysis that is employed by a researcher to conduct research (Mackenzie and Knipe, 2006; Rajasekar, Philominathan and Chinnathambi, 2006; Onwuegbuzie and Frels, 2016). Research methods are also denoted as two different activities in research that involve collection and analysis of data (Tashakkori and Teddlie, 2003). It is paramount for a researcher to be cognisant of what to investigate, in order to primarily guide the chosen method of research. Since this research adopted a convergent parallel databases mixed method design approach, both the quantitative phase, and the qualitative phase were collected in parallel. The aim of this study is to conduct a systematic literature review and examine the determinants and impacts of fish consumption on the incidence and mortality of dementia in older people using a pragmatic research approach.

This study aim was achieved through the following research questions:

- What are the factors influencing the consumption of fish in older people?
- What is the impact of fish consumption on the incidence of dementia?
- What is the impact of fish consumption for survival of older people with dementia?
- What are the perceptions and attitudes of older people about fish consumption and the risk of dementia?
- What are the views of older people about the determining factors influencing the consumption of fish?

The above research questions will be answered using a series of questionnaires and two focus group discussions. These two methods of data collection complement each other by increasing the comprehensiveness and strength of this research.

The following sub-sections provide an overview of the systematic literature review, quantitative and the qualitative designs utilised in this study. This is to justify and clarify the chosen approach in this mixed methods research.

3.6.1 Systematic Literature Review and Meta-analysis

The first phase of this study employed a systematic literature review. This was the preliminary stage of this research, where relevant studies were collected using precise and stipulated eligibility criteria by systematically identifying, choosing and sythesising suitable studies (Liberati *et al.*, 2009). This review is necessary to assess the current evidence on the impacts of fish consumption on the risk of dementia.

A systematic literature review provides a comprehensive summary of existing evidence of published and unpublished studies relating to a specific research question (Armstrong *et al.*, 2011; Siddaway, Wood and Hedges, 2019). The research questions need to be clearly stated prior to the review. The review involves developing a comprehensive database search strategy using the PEO (Population, Exposure and Outcome) framework (Moher *et al.*, 2009). This search strategy should be developed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Moher *et al.,* 2009; 2015). The search should be thoroughly conducted over several databases and grey literature by independent reviewers to identify and synthesise studies that are clearly related to the research question and specified eligibility criteria. The search process must be transparent and carefully conducted to allow replication and reproduction by other researchers. In addition, the relevant studies identified must be critically assessed to establish their quality. Sometimes a meta-analysis is conducted after a systematic literature review.

Meta-analysis involves the combination or pooling of all the reported numerical data from the identified studies in a systematic literature review (Liberati *et al.*, 2009; Siddaway, Wood and Hedges, 2019). Meta-analysis results can improve the effect estimate of the risk factors of a particular disease and resolve differences that could arise from inconsistent study results (Cooper, 2016). Examining the heterogeneity of the studies is very crucial to determine the statistical model to choose for the meta-analysis. This statistical model could either be a random or fixed effect model. The random effect model is used to determine the variability of both within and between studies, while a fixed effect model is used to determine only the within-study variability (Siddaway, Wood and Hedges, 2019).

3.6.2 Quantitative design

The second phase of this study employed a quantitative research approach, where a series of standardised questionnaires were used to collect necessary information from the participants concerning the research questions.

3.6.2.1 Rationale for using questionnaire

Questionnaires were employed in the second phase, because of their ability to collect lots of factual information at once. Questionnaire is generally used to gather an unbiased quantifiable data from people regarding their knowledge, attitudes and behaviour (Boynton and Greenhalgh, 2004). It serves as a means by which the researcher connects with the participants during the data collection process. Questionnaire is a data collection instrument that is cheaper and quicker to administer to a larger and dispersed sampled population and assist in reducing researchers' bias (Mathers, Fox and Hunn, 2007). This survey data collection method allows the researcher to gain access to recruit older people living in the sampled areas of this study, thereby ensuring the anonymity of the recruited participants. This objective process of data collection provides a minute understanding of the subjective experience of older people (Roer-Strier and Kurman, 2009), and there is the need for a pragmatic approach to this research, where the research question plays a crucial role during the research process (Onwuegbuzie and Leech, 2006) as well as permitting the use of another data collection method.

3.6.2.2 Content of the Instruments used for the Quantitative Phase of this study

Questionnaires are crucial tool for collecting data. In this research, validated standardised interviewed-administered questionnaires were utilised to collect the information about the participants' socio-demographic status, disease risk factors, including detailed information of their dietary intakes. These questionnaires include:

The general health and risk factors record derived partly from a previous health and risk factor questionnaire (Chen, Hu and Seaton, 2004), the Minimum Data Set (MDS) of the Medical Research Council Ageing in Liverpool Project-Health Aspects (MRC-ALPHA) study (Wilson *et al.*, 1999; Chen *et al.*, 2009) and the Scottish MONICA surveys (Chen *et al.*, 2003; Chen and Tunstall-Pedoe, 2005): This was used to record the participants socio-demographic information including educational level, main occupation status, annual income satisfaction, smoking status and alcohol intake; social support and relationships; psychosocial aspects, adverse life events occurring in the past two years, personal hobbies, self-assessed physical health and medical history (including awareness and treatment), weight, heights, waist circumference and activities of daily living. Participants provided their dietary intakes details (including rice, wheat flour, meat, fish, egg, fresh vegetable, fruit, chilli pepper, garlic, ginger, and different types of vegetable oils).

Participant's frequency of fish consumption in the past 2 years was recorded at the levels: (1) never eat, (2) ≤ Once a week, (3) >once a week and <daily, (4) Once a day, and (5) ≥Twice a day.

The Geriatric Mental State Questionnaire-Automated Geriatric Examination for Computer Assisted Taxonomy (GMS-AGECAT) a comprehensive semi-structured mental state interviewed administered questionnaire that has been extensively used and validated globally among older populations was used to diagnose the participant's dementia and depression status at diagnosis levels: 0 (well), 1-2 (sub-case), and 3-5 (case). The following demonstrate the way the diagnosis was carried out. The information from the GMS that was primarily collected to identify the mental disorders in the study participants was analysed using the computer program assisted diagnosis AGECAT. This was developed by adopting a theoretical model and its success tested through replication of the diagnoses performed on the psychiatrist's samples. It tried to imitate the way a psychiatrist established a syndromal and differential diagnosis. The symptoms in GMS are combined into a hundred and fifty ‘‘symptoms components’’. Firstly, these symptom components are pooled together into groups characterised by each diagnostic syndrome major symptom areas. The scores on each of the groups signify the final syndromal level of ‘‘confidence of diagnosis’’. The allocation of participants to the levels of confidence by the system was based on both quantitative and qualitative measures, and many clinical decisions were required during the construction for the placement of sets of symptoms components on the syndrome levels. Each participant was assigned to the confidence of diagnosis levels 0–5 for each of the eight diagnostic syndromes including organic disorder, dementia, depression, mania, schizophrenia and paranoia, obsessional, phobic, hypochondriacal and general anxiety. Secondly, the various syndrome levels are compared with one another to achieve a final differential diagnosis at a confidence of diagnosis levels 0-5. A “case level” is mainly designated as ≥3 which resemble a level of severity that requires clinical intervention by psychiatrists. Levels 1 and 2 are designated as ‘subcases’, whereas level 0 (no confidence level on any syndrome) is classified as ‘well’ (Copeland *et al.,* 1999). The GMS-AGECAT dementia ‘‘case’’ diagnoses have been compared with psychiatrists’ diagnoses, DSM III and DSM IV criteria. This has been applied with good levels of agreement in various setting (Copeland *et al.,* 2002, Prince *et al.,* 2003; 2004). This GMS-AGECAT diagnosis has been extensively used worldwide to diagnosis mental disorders in older people (Copeland *et al.,* 2002). Other validated components of the 10/66 algorithm dementia research package (Copeland *et al.,* 2002; Prince *et al.,* 2003) including the Community Screening Instrument for Dementia (CSI-D, part A) cognitive test score (COG-SCORE), Informant questionnaire (CSI-D, part B) (RELSCORE) and the modified Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) ten-word list learning task with delayed recall (Prince *et al.,* 2003; Prince *et al.,* 2008). The 10/66 algorithms analyse the data from GMS-AGECAT and CSI-D to produce a probability of dementia for each participant using a cut-off point (≥0.25) which has been validated in China and among older people in other low- and middle-income countries with low educational levels (Rodriguez *et al.,* 2008).

The local residential areas were visited to obtain information about participants’ survival status through resident committees, village/district leaders, local police stations, family members, neighbours and friends. The electronic registration databases from the Centre for Disease Control and Police Registration were reviewed to identify mortality and causes of deaths in the urban cohort. A standard verbal autopsy questionnaire was employed to further identify other causes of death from family members, relatives, neighbours or friends of the deceased (Chen *et al.,* 2014).

3.6.2.3 Study Location for the quantitative phase

The quantitative phase of this study was conducted in six provinces (Anhui, Guangdong, Heilongjiang, Shanghai, Shanxi and Hubei) in China (See Figure 3.2).

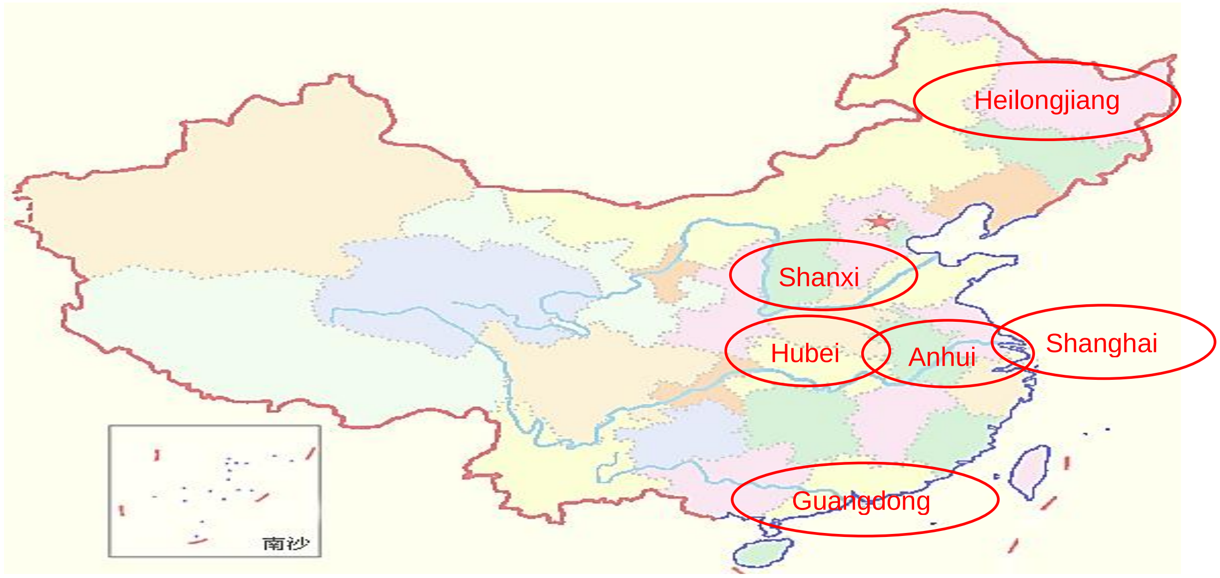


Figure 3.3: Map Showing the Study Location in China

3.6.2.4 Study Population

The study population for the quantitative phase of this study was drawn among older people aged ≥60 years old from six provinces (Anhui, Guangdong, Heilongjiang, Shanghai, Shanxi and Hubei) in China.

3.6.2.5 Sampling Techniques

In research the chosen sampling technique mostly depends on the availability of adequate funds and the nature of the research question, but all the existing method have their uniqueness and relevance. In the quantitative phase of this study, the study participants were randomly selected using a probability cluster randomised sampling technique, while a convenient non-probability sampling technique was utilised in the qualitative phase of this study, since this study adopted a mixed methods design.

Cluster randomised sampling technique involves the use of subgroups of population as sampling unit called clusters that are randomly selected to participate in a study. This could be either a single-stage or two-stage cluster. This sampling method is quite efficient in sampling an extensive geographical area, which was the reason for being used in this study to sample the six provinces in China. However, it has its limitation. This includes an increased risk of bias and sampling error, if the selected clusters do not properly represent the population sampled.

Convenient sampling technique also called haphazard or accidental sampling base the sampling decision on the discretion of the researcher. A researcher may therefore target and select a representative sample that is easily accessible/available and suits the purpose of the research (Etikan, Musa and Alkassim, 2016). This sampling method could be time and cost effective and very convenient and suitable for qualitative study, but it is susceptible to volunteer bias and findings might be non-representative. This was utilised in the qualitative phase of this study to overcome the researcher's time constraint.

3.6.2.6 Data Collection for the Quantitative Phase

3.6.2.6.1 Recruitment and Selection of Participants – Quantitative Phase

3.6.2.6.2 Anhui cohort study

At baseline, 1810 people over 65 years old who had lived more than five years in Yiming subdistrict of Hefei city (Chen *et al.,* 2004; Chen *et al.*, 2012) and 1709 over 60 years old from all

16 villages in Tangdian district of Yingshang county were randomly recruited in 2001 and 2003 respectively (Chen *et al.,* 2005). Based on the residency registration list in each of this selected district in the Anhui province, a total of 3336 adults agreed to participate in this study (response rate of 94.8%), of whom 1736 were living in urban and 1600 in rural area. One year after baseline, 2806 surviving participants (Wave 2) were re-examined. In 2007-2009 (6 years after baseline), 1757 survivors were successfully re-interviewed (Wave 3) (Chen *et al.,* 2014). In 2011-2012, a followed-up data was collected from a total of 944 surviving cohort members using the same interview materials, and 70 deaths were recorded (Wave 4).

3.6.2.6.3 Four-Province cohort study

In 2008-2009, one rural and one urban community from each of the four provinces (Guangdong, Heilongjiang, Shanghai, Shanxi) were selected as the study fields. We tried to recruit no fewer than 500 participants in each community and employed a cluster randomised sampling method to choose residential communities (the district in urban areas and the village in rural) from each of the four provinces; in Guandong, Jitang subdistrict in Huangpu district in Guangzhou city and Lianfeng village in Zhongshan county; in Heilongjiang, Dayou subdistrict in Daowai district in Harbin and four villages in Xianfeng township in Suihua; in Shanghai, a subdistrict (Xietu Road) in Xuhui district and two villages in Xingta township; in Shanxi, a subdistrict in Jinzhong and five villages in Zhuangzi township. The target population consisted of residents aged ≥60 years living in the area for at least 5 years. Based on the residency list of the committees of the village and the district, we recruited a total of 4314 participants with an overall response rate of 93.8% (Wave 1). All the participants were interviewed by trained medical survey teams in each province. At the Anhui Medical University, two researchers from each province were trained. The skills acquired were later cascaded to the local research teams that trained the interviewers.

In 2011-2012, a followed-up data was collected from a total of 2892 surviving cohort members using the same interview materials, and 259 deaths were recorded (Wave 2).

3.6.2.6.4 Hubei cross-sectional health survey study

In 2010-2011, the project was extended to Hubei province (Chen *et al.,* 2014), where Maojian subdistrict in Shiyan city and Yanhe village in Wushan township of Wucheng County were selected as the study area. Overall, 1,001 participants aged ≥ 60 years were recruited and a response rate of 91.8% was achieved.

3.6.2.7 Data Collection procedure for the Quantitative Phase

The quantitative phase of this study was based on an existing secondary cohort dataset from China. The cohort consists of 6071 people aged ≥ 60 years, who were randomly selected from five provinces (Anhui, Guangdong, Heilongjiang, Shanghai and Shanxi). In 2007-2009 these participants were examined for baseline information, with an overall response rate of >90%. The local trained survey team from the Medical Universities in each of the provinces interviewed the participants at home. Permission for interview and written informed consent were obtained from each participant, but in the case of any impossibility, the closest responsible relative or carer were approached to provide assent to participation. Refusals were respected. Each participant provided information about their socio-demographic, and disease risk factors, including detailed information of their dietary intakes. The main interview materials included the general health and risk factors record (Chen *et al.,* 2012; Chen *et al.,* 2013; Chen *et al.,* 2015), the Geriatric Mental State (GMS) questionnaire (Chen *et al.,* 2012), and other validated components of the 10/66 algorithm dementia research package (Copeland *et al.,* 2002; Prince *et al.,* 2003). Using standard procedure, participants' anthropometric data including height, weight, waist circumference and blood pressure were measured (Chen *et al.*, 2003; Chen and Tunstall-Pedoe, 2005). There were 326 participants with dementia, which was diagnosed using the 10/66 algorithm dementia research package (Prince *et al.*, 2003). In the general health and risk factors section, information about socio-demographic, lifestyle, dietary intakes (rice, wheat flour, meat, fish, egg, fresh vegetable, fruit, chilli, garlic, ginger, pepper, and different types of vegetable oils), social networks and support, and histories of chronic diseases were recorded. In 2011-2012, a followed-up data was collected from a total of 3836 surviving cohort members using the same interview materials, and 329 deaths were recorded.

3.6.2.8 Data Analysis for the Quantitative Phase

The baseline and follow-up data were checked, coded, and cleaned before it was analysed using the Statistical Package for Social Science (SPSS). Descriptive statistics was used to examine the mean and standard deviation of continuous variables (e.g. age) and percentage for categorical variables, including fish consumption. Distributions of baseline risk factors and health conditions among participants with different level of fish consumptions documented in wave 3 survey were examined using one-way analysis of variance (ANOVA) for continuous outcome variables and chi-square test for categorical variables. Binomial logistic regression models were employed to examine the determinants of older people having any level of fish consumption versus those who stated they “never eat” fish over the past two years. We calculated the odds ratio (OR) and 95% confidence intervals of each baseline risk factor associated with the consumption of fish in a 6-year follow up. In the models, we adjusted for age and sex first, to compute the OR. We further examined those variables that were significant in the age-sex adjusted analysis, with multivariate adjustment including waist circumference and smoking at the baseline (see appendix 11 for syntax for data analysis in chapter 5).

Binary logistic regression model was employed to calculate the odd ratio (OR) and their 95% confidence intervals (CI) of dementia in participants with different levels of fish consumption in comparison to those with no fish consumption over the past two years, adjusting for age, sex, provinces, urban/rural areas, educational level, smoking status and stroke in the model (see appendix 11 for syntax for data analysis in chapter 6).

Multivariate adjusted binary logistic regression models were employed to assess the risk of incident dementia in relation to any levels of fish consumption over the past two years, adjusting for age (cont.), sex, province, urban-rural, educational level, body mass index (BMI), smoking status, and alcohol consumption, marital status, frequency of visiting children or other relatives, hypertension (yes or no), diabetes, heart disease, stroke, activity of daily living and depression, dietary intake: e.g. meat and egg, vegetable and fruit consumption (see appendix 11 for syntax for data analysis in chapter 7).

Multivariate adjusted Cox regression models were employed to calculate the hazard ratios (HR) of all-cause mortality and mortality in people with and without dementia in each of the fish consumption level, adjusting for age (cont.), sex, body mass index (BMI), smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives, hypertension, heart disease, diabetes, activity of daily living, depression and cognitive impairment/dementia, dietary intake: e.g. meat, fish, egg, vegetable, fruit (see appendix 11 for syntax for data analysis in chapter 8).

Meta-analysis was performed by pooling all the data that include the odds ratios, rate ratio or hazard ratios and their 95% confidence interval (CI) from published studies and the new community-based cross-sectional and cohort study together and analysed using the STATA version 14.2 statistical software package. A random effect model was employed if the heterogeneity of the within and between studies variation were significant; otherwise, a fixed effect model was used. Heterogeneity across the studies was evaluated using the I^2 statistic, where I^2 statistic of less than 25% signifies a small degree of inconsistency while greater than 50% signifies a large degree of inconsistency (Higgins *et al.,* 2003; Ioannidis *et al.*, 2007). Publication bias was evaluated using the Egger's regression (Egger *et al.,* 1997).

3.6.3 Qualitative design

Alongside the quantitative data collection phase in this study, the qualitative phase was conducted. This qualitative phase in connection with the quantitative phase aimed to provide a comprehensive interpretation of the research questions (Bryman, 2006). This qualitative research method involves understanding a social phenomenon from the viewpoint of those concerned, to positively transform the social conditions (Glesne, 2010). This is aimed at interpreting the words of the informants in the social environment. This qualitative data collection phase employed a semi-structured discussion guide (see appendix 5) to collect data from the participants that consented to participate in the two focus group discussions (see appendix 7 for consent form) and analysed using a thematic analysis approach highlighted in Braun and Clark (2006).

3.6.3.1 Scope of the study

The qualitative part of this research was carried out entirely in a religious organisation based in Wolverhampton the United Kingdom (UK), since the people there fall within the target age group. It was expected that the research findings will be applicable to other related settings and group of people. The findings should complement the quantitative part of this research about the reasons why people consume (or do not consume) fish and to know whether they are aware of its beneficial impact on health especially in reducing the risk of dementia.

3.6.3.2 Focus Group Discussion

Focus group discussion (FGD), a qualitative design method, was employed in this part of the research. Focus group was defined as a form of informal discussion among designated group of people about a specific topic (Wilkinson, 2004). This method is primarily used to explore peoples' views and perception through discussion among group members. This method allows people to express their opinion and explore their knowledge and experiences about the topic of discourse (Kitzinger, 1995). This study design uses words instead of numbers as a form of data collection through documenting people's views (Stalmeijer, McNaughton and Van Mook, 2014). FGD is a suitable method used for collecting sensitive information through the contribution of the participating members of the discussion group (Stalmeijer, McNaughton and Van Mook, 2014). FGD encourages and enables contributions from all the participating members in the group. According to Krueger and Casey (2000), a standard FGD must include at least 6 to 8 participants depending on the wealth of information required to be collected. Likewise, Krueger and Casey (2014) emphasised that FGD must contain an optimum number of between 5 to 10 participants, which is a recommended manageable number of participants that is required to avoid disorderliness, while being able to explore and gather different perspectives of people about the topic of discussion.

FGD was chosen as the research method for the qualitative part of this research because it tends to be more productive compared to the interview method. FGD allows data to be collected within a short period of time compared to the time required to conduct a one-to-one interview. Also, it provides an opportunity for the participants to critically comments on the topic of discourse and allows group members to share common experiences and feelings, thus generating a deep and enriched data during the interactive session (Thomas *et al.,* 1995; Stalmeijer, McNaughton and Van Mook, 2014). On the other hand, FGD consume a lot of time, especially at the data transcription stage due to participants talking over one another and at the analyses stage (Boyce and Neale, 2006). There is also the tendency for some of the participants to dominate the conversation, by denying the shy ones the opportunity to contribute. To achieve a thorough process of discussion, the participants are expected to have background knowledge of the subject matter.

3.6.3.3 Study Location for the Qualitative Phase

The qualitative part of this study was conducted in the Wolverhampton area of the West Midlands, UK. Wolverhampton is a city with an extremely diverse religious and cultural background and an ageing population of slightly over 50,000 older adults aged ≥ 60 years, which represent approximately 22% of the overall population (WPIS, 2014).

3.6.3.4 Data Collection for the Qualitative Phase

3.6.3.4.1 Recruitment, Study Participants and Sampling

The study target population were community dwelling older adults aged 60 and above that reside in Wolverhampton area of the West Midlands, UK. I was particularly interested in this group because people over 60 years are at an increased risk of having dementia and cardiovascular disease. In 2018, a convenient non-probability sample of 6 to 8 older adults was targeted and recruited to participate in this study, according to Krueger and Casey (2000; 2014) recommendation. This number of participants was required to allow diverse expression of peoples' views and avoid fragmentation and disorderliness. The recruitment was achieved through word of mouth in a local religious organisation especially among the members of a designated place of worship. This setting was chosen because it had a diverse group of people from different cultural backgrounds.

An invitation letter (Appendix 4) explaining the purpose of the research was sent out via email through the head of the congregation to the members of a designated place of worship to capture those that were interested in participating. Information about the research also appeared in the organisation's newsletter to increase the visibility and attract more interested participants. The members that showed interest to participate were asked to contact the researcher via her university email address or telephone, but those that prefer not to be involved were advised to destroy/disregard the letter. To be eligible to participate in the FGD, the participants were expected to be aged 60 years and above, have no history of dementia or diagnosis and were willing and able to consent to participate in the study. Those potential participants that were unable to consent, automatically became ineligible to participate and they were neither contacted nor involved in the study.

Out of 18 adults who showed an expression of interest in taking part in this study, 12 adults agreed and consented to participate in the two discussions after many weeks of trying to recruit. The participants were divided into two equal groups of six participants each for the two FGD sessions. No definite criteria were used to allocate the participants into the two FGDs, except specifically through expression of interest, availability of the participating members and participant having schedule that fit into the set dates and times for the study data collection. As soon as the 6 available spaces for the first FGD session were full, the 6 remaining participants were automatically assigned into the second FGD session that took place three weeks after the first session. Therefore, the participants in each of the FGD session were different but the same topic was discussed. Participants were briefed about the research through written information sheet (Appendix 8) (seen and through phone call and text messages) once the participants have confirmed their attendance via email. To achieve a thorough exploration of the research question and produce quality data, two focus group discussions were performed. According to Krueger and Casey (2014) recommendation, three to four FGDs is enough to achieve a theoretical saturation for a simple research question. However, due to the difficulty faced to get enough interested participants and the time constraint of the research, only two FGDs with different participants were feasible. These two FGDs were carefully performed to enhance the generation of reliable and valuable data that could thoroughly answer the research question.

In qualitative research, data saturation involves achieving the research purpose through accumulation of different views, which differs from the statistical parameters popular with quantitative research (Francis *et al.*, 2010). Therefore, complete data saturation was achieved when no new themes, findings and concepts were generated from the discussions (Bowen, 2008).

3.6.3.4.2 Materials/Data Collection

Adhering to the principle of conducting focus group discussion (Krueger, 1998), a semi-structured discussion guide aimed at elucidating the health benefit and the reason why people consume fish as well as the factors that affect its consumption was developed and used to collect the required information. This discussion guide (Appendix 5) allows the discussion of the predetermined topics as well as other topics that emerge as the discussion progresses. The questions were open-ended to encourage free flow of ideas, gain trust and develop rapport with participants and this was developed based upon relevant literature (Krueger and Casey, 2014). After the development of the questions, it was tested within and revised if necessary and later pilot-tested among five people of similar age with participants, but independent of the focus groups to ensure the questions fit with the proposed aim of the study. This pre-test provided the researcher the opportunity to receive valuable feedback from the participating group by ensuring the questions were easily understood and the data generated were appropriate (Tashakkori and Teddlie, 2009). This process provided the researcher the experience required in conducting a focus group discussion and to determine the approximate timescale required to complete the discussion. It also facilitated the assessment of the discussion guide to ensure the appropriate questions that can provide the required answers were asked.

This data collection method was chosen to ensure the views and perceptions of the participants were captured throughout the discussion. The discussion guide includes an introductory part that sensitised the participants reasoning and allow them to get acquainted with the discussion. The other part that comprises of the key questions was used to direct the group discussion towards the main objective of the study. Throughout the two discussions the moderator (A.T) ensured the discussion guide was followed but introduced prompt and probe questions when necessary during the discussion to allow for clarifications and deeper exploration, while also ensuring enough flexibility for unexpected themes to emerge as the discussion progressed.

3.6.3.4.3 Data Collection Procedure

The FGD was organised at one meeting room that could accommodate 9 participants in the Millennium City (MC) building of the University of Wolverhampton, situated in the West Midland UK at a time and date convenient for the participants and the researcher. This location was easily accessible for the participants since it is secure and near to their regular place of worship. The aim of the study was explained to the participants and they were asked to sign informed written consent to confirm that they understood the study and what was expected of them, and that they agree to take part. This was necessary to ensure anxiety, distractions and embarrassment was avoided during the discussion, which could affect the quality of a good focus group. Before the commencement of the focus group, the researcher established rapport with all the participants and ensured the room was comfortable and distraction free. At that point, each participant was asked to complete a brief questionnaire that comprises of their demographic data to identify whether the sample represents a wide population or whether there was presence of bias (see Appendix 6). The two focus group discussions lasted for approximately 60 minutes each and took place three weeks apart. They were facilitated by the researcher (moderator) and a co-moderator (researcher's colleague), but the researcher supervisor was present for a brief introduction and welcoming of the participants before the commencement of the discussions. The two moderators took notes throughout the discussions as backup plan and ensured all the participants were encouraged to contribute to the discussion and their views were documented. Despite this opportunity and encouragement given to participants, some participants within the group dominated the discussion by expressing their views, while few of them hesitated. These episodes were resolved through proper facilitation of the discussion by highlighting the importance of allowing all the group members to participate in the discussion while encouraging and giving the hesitant participants the opportunity to express their views through prompt usage. The discussions were audiotaped with the consent of the participants. Two audiotapes were utilised during the focus group, where one acted as the main and the other serves as a backup to avoid any unforeseen circumstance i.e. device failure. Participants were provided with hot drinks and snacks during the discussions and lunch afterwards but were not financially reimbursed or rewarded for their contributions. Prior to the commencement of the focus groups the participants were again reminded and informed of their right to withdraw from the discussion at any time.

3.6.3.4.4 Data Analysis for the Qualitative Phase

Data analysis is a very crucial stage in focus group research, because it helps to convert the collected data into valuable piece of information, provided the research questions are answered using appropriate analysis technique. In qualitative research huge amount of data are produced, which provide understanding to the various changes that can be implemented in future (May and Pope, 2000). This section summaries the procedure for focus group discussion data analysis using thematic analysis.

The participants' background information that comprises of age, sex, marital status, income, occupational class, educational background, and ethnicity were collected to establish the demographic data of the participants. This was stored and organised using the Nvivo version 11 qualitative software program. The focus group audio recordings were uploaded onto the computer using the Nvivo version 11 qualitative software program and manually transcribed verbatim by the researcher into Microsoft Word. Throughout the transcript, the participants' names were anonymised using pseudonyms to ensure confidentiality. The transcripts were reviewed at least three times by the researcher through checking for accuracy and completeness, and any important points that were written in the field notes by the moderator during the focus group discussions were used separately. The researcher read the transcripts and listened to the audio tapes repeatedly. The Nvivo version 11 qualitative software program was used to organise, store and manage the data during transcription before manually embarking on thematic analysis, the chosen data analysis technique.

3.6.3.4.5 Thematic Analysis Process

Thematic analysis was adopted to analyse the collected focus group discussion data. Thematic analysis involves the fragmentation, categorisation, organisation and reconnection of coded data before they are finally interpreted (Grbich, 2007). It is a process of identification, analysis, reporting and interpretation of identified themes that are important within the transcribed data (Braun and Clarke, 2006).

Themes are vital chunks of data embedded within a dataset which generally provide answers to the research questions (Braun and Clarke, 2006). This part of the research is exploratory in design, and thereby employed the use of an inductive analytical approach (bottom-up approach). This method of analysis provides the opportunity to discover chunks of data that repeatedly occur within the transcript. Using the thematic method of analysis allow the proper interpretation of different features of the research topic and enrich the data through extraction of relevant and necessary themes, thus allowing a rich description of the data (Blacker, 2009). The analysis techniques do not depend on a specific epistemological stance or theoretical position rather concerned with the interest of the researcher on ways of answering the research question (Braun and Clarke, 2006). It, therefore, makes this thematic analysis method flexible to use in any other theoretical frameworks by allowing easy generation of themes through using an inductive or deductive method. Although thematic analysis is widely used, some still perceived it as a foundational tool rather than a main method of analysis (Boyatzis, 1988). Fundamentally, most analyses are thematic in nature, but some researcher refers to it as another thing (Fielden *et al.*, 2000; Braun and Clarke, 2006). This could occur due to inadequate reporting of a research analyses process, which therefore makes the research difficult to evaluate or open to comparison with other similar research work. The exclusive reporting of emerging themes from a data or simply “themes discovery” demonstrate the process of analysis and its accountability (Taylor and Ussher, 2001). This ensures the avoidance of researcher's interest and bias during the process of identification, selection and reporting of the themes. Therefore, a good research must demonstrate the guiding principle and detailed epistemological stance that was followed during the research process (Crotty, 2009). This was considered throughout the execution of this current research.

Due to the flexibility involved in using thematic analysis, no specific guidelines are followed, but the data need to be transcribed verbatim to ensure all the required information is included (Braun and Clarke, 2006). A rich thematic account of the collected data is important to achieve the aim of this study (Braun and Clarke, 2006) so that its readers can have an idea of the significant themes raised by the participants. Therefore, the transcribed discussions were analysed using thematic analysis (Braun and Clarke, 2006).

Phase 1: Familiarisation with the data: The focus group data analysis began by familiarising with the data during the interactive focus groups data collection and transcription. Following the data transcription, a thorough immersion in the dataset was carried out by the researcher through reading and re-reading of the transcript and getting acquainted with the emerging pattern while carefully taking notes of relevant ideas.

Phase 2: Initial codes generation: Relevant information from the dataset that may form important themes are identified through coding. Codes are described as the component of the raw dataset that seems fascinating and can be meaningfully assessed considering the phenomenon (Braun and Clarke, 2006). To generate the codes, the researcher highlighted and labelled all important features that expressed the views and perceptions of each FGD participants on the research topic through identification of relevant extracts that could answer the research questions. The generated codes served as the foundation for the development of the subthemes. Instead of adopting a theory-driven themes mode of coding that entails focusing on certain questions that were asked during the FGD, a general mode of coding was adopted to support a data-driven themes generation. This approach was required due to the nature of the topic and to accommodate the several overlaps of responses from the participants that occurred during the discussions. Therefore, to ensure the data produce several possible themes, the researcher systematically coded interesting features that were applicable to the research questions throughout the entire data manually. Adhering to Bryman (2001) recommendation, the researcher ensures the surrounding extracts of the data were included in the coding to circumvent losing the context of the generated codes.

Phase 3: Searching for themes: The researcher collated and sorted all the generated codes into subthemes and assembled all the coded data relating to each subtheme together. Since, themes emerge when ideas occur repeatedly in the data, the possible subthemes that could eventually graduate into overarching themes were gradually gathered by the researcher through careful collation of all codes considered relevant to the research question and organised using an excel spreadsheet. The researcher examined the codes for any recurrent themes, and the codes that were similar were grouped together to make some overall concepts and later categorised into key themes. To aid sorting of different codes into subthemes, the researcher applied a variety of colours to the codes and they were visually represented. The different ideas that appeared under each of the key themes were categorised and summarised. Thematic maps were employed to demonstrate the connections that exist between the various codes, the subthemes at different levels, and the potential overarching themes. Even though majority of the codes fitted into specific subthemes, some of them were discarded, while others were temporarily accommodated since they could not fit anywhere.

Phase 4: Reviewing themes: The researcher checked if the generated themes match the relevant coded extracts. Following this step, the thematic analysis map was developed, where several subthemes were refined and combined to form one broad theme. The researcher further re-read the transcript severally to ensure the generated themes properly fit together and to ascertain the initially missed relevant data were coded. The completion of this phase reveals a clearer overview of all the emergent themes and how they collectively fit together to tell a story.

Phase 5: Defining and naming themes: It is essential that the themes were refined and defined clearly, by generating specific names that reflect the meaning of each theme. Therefore, the generated thematic maps were cautiously scrutinised through identification of what the themes signified and the story surrounding each theme. A thorough analysis and an explanation of what each theme portrayed was performed. This is to ascertain they are well fitted with the subthemes and the associated coded data extracts while avoiding any overlap.

Phase 6: Producing the report: This final stage was accomplished through the selection of the required and correct data extracts to illustrate the emerging themes by referring to the literature and research question. This entails report writing through using direct quotes that represent the different opinions of the participants to illustrate the emerging themes. The discussions were then synthesised through reviewing the written notes of the moderator, identifying the recurrent ideas from the discussion, and interpreting the recurrent thoughts in relation to other themes that occurred during the discussion.

These were categorised into five major themes: Fish consumption habits, perceived enablers/barriers of fish consumption, perceived benefit of eating fish, commonly consumed fish, and participants' concerns (See Appendix 9 for specimen of focus group discussion transcript).

3.7 Trustworthiness in Research

Trustworthiness in research involves using rigorous approach to accomplish the specific research objectives through application of appropriate research instruments (May and Pope, 1995). Therefore, the quality of this research was guaranteed by ensuring trustworthiness throughout the research process through adequate description of the research procedure and maintenance of the standards of research (Frambach, van der Vleuten, and Durning, 2013). Trustworthiness of this research was achieved by employing the Lincoln and Guba (1985) four essential criteria. These include credibility, confirmability, dependability and transferability. They all describe the steps taken to attain trustworthiness in qualitative research. The following sections demonstrate how trustworthiness was achieved in this study.

3.7.1 Credibility

Credibility is the declaration about the truth of the research findings (Polit and Beck, 2008; Anney, 2014). It acknowledges whether the findings of a study are a true representation of the original data and the views of the participants (Lincoln and Guba, 1985). The credibility of this study was ensured by utilising some of the strategies outlined by Lincoln (1995), which include peer debriefing, prolonged engagement with the participants and audit trail.

Peer debriefing was accomplished through communication of the finding's and its interpretation with my supervisory team at every data analysis phase and presentation of findings within the university.

Prolonged engagement was established during the research through rapport development with the research participants. This was achieved by attending two of the Sunday church services of where the participants were recruited to build rapport with the prospective participants through explanation of the purpose of the research.

Audit trail of the research was achieved through keeping notes that contain the interpretation of the findings during the data analysis.

3.7.2 Transferability

Transferability represents the rate at which the research findings are applicable to other settings using different respondents (Lincoln and Guba, 1985; Anney, 2014). This involves adequate and thorough description of a study to enable easy appraisal of how transferable the conclusion is to other settings and people (Denzin, 2001; Denzin and Lincoln 2005; Stalmeijer, McNaughton, and Van Mook, 2014). Therefore, this study provided detailed rationale for the research, justification for the choice of method, instrument adopted, analysis method, study locations and participants to ensure proper and adequate evaluation for transferability was ascertained.

3.7.3 Dependability

Dependability involves the ability of a research to give similar results when conducted in a similar setting with similar participants under the same condition (Polit and Beck, 2008). This reflects consistency in the findings over a period of time (Anney, 2014). This study established dependability through external auditing. This process of auditing involves the use of a neutral researcher that is not involved in the study to evaluate the research process. This is required to ascertain if the findings and its interpretation is in accordance with the data (Lincoln and Guba, 1985; Cope, 2014). This external auditing process was accomplished through rigorous supervision received from my supervisory team. This ensured consistency and clear reporting throughout the research and repeatability to attain similar results assuming the research is repeated.

3.7.4 Confirmability

Confirmability denotes the rate at which the findings of a research can be verified or validated by other researchers to ensure the findings is a true representation of the participants viewpoint without the interference of researcher's motivation, interest and bias (Polit and Beck, 2008; Anney, 2014). Confirmability of this research was accomplished through provision of detailed description of the data analysis process to ascertain the findings were from the raw data and participants views were supported by direct extract from the data and finally audited externally by the supervisory team.

3.8 Ethical considerations

Ethical permission for the cohort study data collection was obtained from the Research Ethics Committee of Anhui Medical University in China, the Research Ethics Committee of the University College London, UK, and the Research Ethics Committee of the School of Health, University of Wolverhampton. This study has been ethically approved by the Research Ethics Committee of the Faculty of Education, Health and Wellbeing, University of Wolverhampton, UK (Appendix 1) following minor revisions. Confidentiality of this research was preserved by the researcher by ensuring that only the researcher and the research members have access to the responses of the participants. Also, proper provision was made to avoid linking each response to the participants to ensure anonymity. This research did not collect any identifying facts about the study participants, except that which was necessary to answer the research question and they were coded to avoid any identification. For instance, their names, and email addresses. Although, there was collection of participants' demographic data using a brief questionnaire, this did not reflect any of their names to ensure confidentiality. Participants' personal data including the completed brief questionnaires and transcripts from the audio tapes were stored in a hard drive on a password protected personal laptop and backed up copy on an external hard drive and memory stick, and securely stored in my supervisors' computers. This will be securely kept in a locked location for 2 years immediately after the study according to the University of Wolverhampton regulation on data storage. Informed consent form was provided for the participants (Appendix 7) after explaining the purpose of the study and ensuring the proper understanding of the content. The participants confirmed in writing by signing the consent form on the day of the focus group discussion, after they have read and understood the participants information sheet (Appendix 8) that explains their rights to confidentiality, considered what they are expected to do and are satisfied with participating. Also, the participants were asked to confirm that they are aware that participating in the study is voluntary, and they can withdraw at any point during the research without any penalty or rights affected. They also confirmed that no one coerced them to participate.

3.9 Summary

This chapter demonstrates the quantitative and qualitative research methodology and design employed in this study. It highlighted the philosophical assumption, data collection and analysis process, and the ethical considerations employed in this study. It emphasises the rationale behind choosing a mixed methods research design to answer the research questions as well as using focus group discussions and questionnaire as the method of data collection. The data analysis for the quantitative phase employed descriptive and inferential statistic, while thematic analysis was used for the qualitative phase of this study. Finally, the trustworthiness of the data used in this study was discussed. The following sections present the chapters containing the findings of this research.

CHAPTER FOUR: ASSOCIATION OF FISH CONSUMPTION IN OLDER AGE WITH DEMENTIA: A SYSTEMATIC LITERATURE REVIEW

4.1 Introduction

There is increasing evidence in epidemiological studies of the role nutrition particularly fish consumption plays in delaying or preventing dementia. Fish is a nutritional source of high-quality animal protein, with various essential nutrients (Lund, 2013; FAO, 2018). It is the major dietary source of long-chain omega-3 polyunsaturated fatty acids (PUFAs) with various protective health properties including neuroprotection (Bazan, 2006; Innis, 2007), antithrombotic (Saravanan *et al.*, 2010) and anti-inflammatory properties (Calder, 2013). Although previous studies suggested that increased consumption of fish reduces the risk of cardiovascular diseases (Bonaccio *et al.*, 2017) and depression (Li, Liu and Zhang, 2016), but its association with the risk of dementia is unclear. Some studies suggested that increased consumption of fish was associated with a reduced risk of dementia (Barberger-Gateau *et al.*, 2002; Morris *et al.*, 2003), while others did not show such an association (Engelhart *et al.*, 2002; van de Rest *et al.*, 2009). Due to the inconclusive findings of the impact of fish consumption on the risk of dementia, previous systematic literature review has not been thoroughly conducted (Fotuhi, Mohassel, Yaffe, 2009; Solfrizzi *et al.*, 2017; Roman *et al.*, 2019). Therefore, we carried out a new comprehensive systematic worldwide literature review of current evidence to investigate and ascertain the association of fish consumption and the risk of dementia.

4.2 Methods

4.2.1 Data Sources and Studies selection process

We (Aishat Bakre and Isaac Danat) independently searched and re-searched literature from the MEDLINE, PubMed, CINAHL, PsychINFO, and Psychology and Behavioural Sciences

Collection databases. The strategy for the database search was developed using the PEO (Population, Exposure and Outcome) framework (Moher *et al.,* 2009). The search terms were [‘dementia’ OR ‘Alzheimer’s disease’] AND [‘fish’]. The literature was searched from the earliest date of each of the databases to 30 November 2016. The search for relevant articles included all studies with no language restriction. We read the title and abstract of the searched studies. The studies selected were appropriate for the current review if they investigated an association between fish consumption and dementia or Alzheimer’s disease (AD) in the population. Alongside the electronic database search, a manual reference search was also conducted to find additional articles missed by the online search. If two articles were published from the same cohort data but in different follow-up durations (Kalmijn *et al.,* 1997; Devore *et al.,* 2009), we used the article from the longest follow-up study for review (Devore *et al*., 2009). Figure 6.1 (see chapter 6) shows the study selection process. Eleven original studies were identified eligible for review. Following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Moher *et al.,* 2009; 2015), a systematic review was conducted.

4.2.2 Data extraction and Quality assessment

Each of the articles was reviewed by two reviewers (Aishat Bakre and Isaac Danat) and assessed independently using a predesigned data extraction form to extract the necessary information from the chosen studies. The information extracted includes the first author’s name, publication year, study type, study name, study location, participants’ characteristics, recruitment strategy, sample size, sample size at follow up (% of baseline sample), study duration, baseline measure of frequency of fish consumption, categories of comparison, endpoint outcomes: number of dementia cases; dementia diagnosis criteria, data analysis method, confounders adjusted, and findings including the risk ratios (RRs), odd ratios (ORs), or hazard ratios (HRs) and 95% CIs of dementia and AD. Differences in reviewing literature and extracting data between the two reviewers were resolved through face-to-face discussion; if differences remained, a third reviewer (RC) discussed with them to reach agreement. The quality assessment of the articles was achieved by employing the Newcastle-Ottawa Scale (Wells *et al.,* 2014) to assess the cohort and case-control studies and the AXIS tool (Downes *et al.,* 2016) was used to assess the cross-sectional study (see Table 4.3). The Newcastle-Ottawa Scale (NOS) (Wells *et al.*, 2014) nine components rating scale assesses each article on three broad scales, including the selection bias, comparability and outcome/exposure. Based on specific criteria, a total award of between 0-6 scores was classified as a low-quality study, while 7-9 scores were classified as a high-quality study.

4.3 Results

4.3.1 Review and synthesis of the identified studies

In the eleven identified articles, we found that all were from high income countries, except for one study led by the UK (Albanese *et al.*, 2009) which included seven studied populations from LMIC. They were published between 2002 and 2011. One of the studies was cross-sectional (Albanese et al., 2009), three were case-control (Conquer, 2000; Tully *et al.*, 2003; Kim *et al.*, 2010) and seven were cohort (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005; Schaefer *et al.,* 2006; Barberger-Gateau *et al.,* 2007; Devore *et al.,* 2009; Lopez, Kritz-Silverstein, Barrett-Connor, 2011). These articles included seventeen studied populations since one study (Albanese *et al.*, 2009) consisted of seven populations. Their sample size varied from fifty-seven to 14956, with a total of 33964 participants, and the minimum age in these studies' populations varied from 55 to 76 years. Four of the studies used food frequency questionnaire (FFQ) (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005; Barberger-Gateau *et al.,* 2007), three used a semi quantitative FFQ (SFFQ) (Schaefer *et al.,* 2006; Kim *et al.,* 2010; Lopez, Kritz-Silverstein, Barrett-Connor, 2011), one used a meal-based check list alongside an SFFQ (Devore *et al.,* 2009), and the remaining one used a face-to-face standard method of assessment to evaluate the participant's fish intake (Albanese *et al.,* 2009). Data from the four studied populations reported a statistically significant association of fish consumption with reduced risk of dementia, although two of them (Conquer *et al.,* 2000; Tully *et al.,* 2003) did not present the effect sizes. Data from eleven studied populations showed an association but a non-statistically significant reduction, while two exhibited no association (or increased risk) (Albanese *et al.,* 2009; Devore *et al.,* 2009). Tables 4.1 and 4.2 document the details of the studies' characteristics and outcomes. The descriptive account and the findings of each of the included studies are as follows.

4.3.1.1 Cross-sectional study

Albanese (2009)

The study by Albanese *et al.* (2009) investigated the association of dietary intakes of fish and meat with dementia using the data from 10/66 population-based studies of dementia and aging in 7 Low- and middle-income countries. The study was for 7 countries. Residents aged ≥65 years were listed through door to door knocking and participants recruited in Jan 2003 to Nov 2007 from 11 sites across 7 countries. It included Urban and rural sites (Peru, Mexico, China and India) or Urban sites alone (Cuba, Dominican Republic and Venezuela). The well-off areas were avoided. The 10/66 study protocol questionnaires were used to collect participants' data on socio-demographic, health status, health behaviours, and risk factor exposures as well as physical and neurological examination. The total sample size for the study was 14,960 for all Countries including Cuba (2,934), Dominican Rep (1999), Peru (1927), Venezuela (1939), Mexico (1997), China (2162), and India (1998). Response rates ranged from 80-94%. Face to face interviews using standardised questions on fish and meat intakes per Week were used to gather data for frequency of intake as “never”, “some days”, “most days” and “every day”. Dementia status was assessed using the 10/66 diagnostic algorithm. For the data analysis, Poisson regression was used to calculate unadjusted and adjusted prevalence ratios (PR) for fish and meat consumptions for each Country. Likelihood tests were carried out to test for departures from linearity, and to test for the hypothesis of a linear association between dietary intake and dementia prevalence. The fish/meat intakes of “most days” and “everyday” were collapsed into one category resulting in categorical variables with three levels of intake. Finally, the associations for dietary fish, and meat, with dementia for all countries were summarised in a 2-fixed effect model meta-analysis forest plots.

The results of the crude models from the Poisson regression analysis showed consistent association of fish consumption and dementia prevalence in all countries except India. It ranged from 0.40 (0.26-0.60) in China to 1.13 (0.84-1.50) in India. The crude Prevalence Ratio (PR) was 0.67 (0.52-0.88) for Cuba, 0.74 (0.60-0.91) for Dominican Rep, and 0.83 (0.61-1.14), 1.11 (0.83-1.49), 0.64 (0.49-0.85) for Peru, Venezuela, and Mexico respectively. After adjusting for age, sex and education in the first Model, the inverse association was reduced. The PR was 0.86 (0.68-1.08), 0.77 (0.62-0.94), 0.87 (0.64-1.20), 0.92 (0.69-1.23), 0.83 (0.64-1.08), 0.45 (0.31-0.67) and 1.18 (0.88-1.58) for Cuba, Dominican Rep, Peru, Venezuela, Mexico, China and India respectively. There was no substantial change in PR after further adjustment in model 2 for family history of dementia, chronic diseases, depression, smoking, living arrangement and number of assets. The PRs for model 2 were 0.83 (0.66-1.04), 0.78 (0.64-0.95), 0.84 (0.61-1.14), 0.92 (0.68-1.26), 0.85 (0.65-1.11), 0.50 (0.36-0.71) and 1.18 (0.88-1.59) for Cuba, Dominican Rep, Peru, Venezuela, Mexico, China and India. Additional adjustments including dietary meat, alcohol consumption, diary fruits and vegetables did not substantially change the results. Findings of meat consumption and prevalent dementia were inconsistent across all countries. The PRs were 1.28 (1.04-1.58) in

Cuba and 1.52 (1.16-1.99) in Peru, which remained statistically significant after adjusting for potential confounders. However, the crude PR for China suggested an inverse relationship between meat consumption and the risk of dementia 0.67 (0.50-0.90), which became statistically non-significant after adjustment. The findings from fixed effect meta-analysis showed a combined PR of 1.19 (1.07-1.31) for meat and dementia and 0.81 (0.72-0.91) for fish and dementia, both of which were statistically significant. The study suggested a dose-dependent inverse association between fish consumption and prevalence of dementia that was consistent in all sites except India. They however found a less consistent, dose-dependent and direct association for meat and dementia prevalence.

The study demonstrated high quality based on assessment for cross-sectional design. However, exclusion of more affluent areas within countries for the study affects the generalisation of findings or comparison with those from the West or limits it to people with similar dietary and health features. Random errors with regards to reporting dietary exposures may have led to an underestimation of the true values. Selection bias could also not be excluded which might explain why those without dementia and reporting higher fish intake were more likely to participate in the study.

4.3.1.2 Case-control studies

Kim (2010)

The study by Kim *et al*. (2010) evaluated the consistency of Country-specific hypothesis that n-3 Polyunsaturated Fatty Acids (PUFAs) of erythrocyte such as; α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is associated with mild dementia using a Korean elderly population. The study involved 57 elderly patients (38 females) aged ≥ 65 years, who were recruited between December 2008 and January 2009 from the Kuri area in Korea. The average and frequency of various foods consumption were measured using a 51- item food frequency questionnaire. Measures of portion sizes were aided by full scale photographs, intake was analysed by a Can-pro 3.0 (Korean Nutrition Society, Seoul, Korea). The blood samples from participants were collected, gas chromatography was used to analyse fatty acid methyl esters. Identification of fatty acids was done by comparing with known standards. Erythrocyte fatty acid composition and dietary intake were categorised into tertiles (1, 2 and 3). Dementia diagnosis was done using Mini-Mental Status Examination (Korean version MMSE-K). The MMSE-K score was used to categorise participants into normal group (score>21) and dementia group (score ≤21) containing 24 and 33 participants respectively. Continuous variables were expressed using the mean and the SEM to compare case and control by using an independent t test. The proportions of nominal variables were compared using the χ^2 test. They found that ALA from plant sources of n-3 PUFAs decreased the risk of mild dementia but not the EPA and DHA from fish. A partial correlation analysis with adjustment for age, sex, height and energy intake showed a significant positive correlation of MMSE-K score and fatty acids in erythrocytes for ALA (r=0.459, p<0.001) and total n-3 PUFA (r=0.299, p=0.028). The results were, however, non-significant for DHA (r= 0.231, p=0.093) and EPA (r=0.108, p=0.436). A multivariate logistic regression, with adjustment for age, sex, height and energy intake showed a significant reduction in the risk for mild dementia (OR 0.09, 95%CI 0.01-0.94) for the highest tertile and non-significant association for the middle tertile 0.36 (0.05-2.84) when compared with lowest tertile of α-linolenic acid (ALA). A non-significant risk reduction was observed for n-3 PUFA for the highest (OR 0.68, 0.12-3.77) and middle tertile 0.53 (0.09-3.18). The finding was similar in the DHA for the highest (OR 0.70, 0.13-3.75) and middle 0.46 (0.07-3.08) tertile. However, in the case of EPA there was non-significant increase in the risk of mild dementia for the highest (OR 1.61, 0.22-11.94) and middle 3.53 (0.52-24.020) tertile. The study adjusted for very few covariates, with education not controlled in the analysis even though it is known to influence dementia risk. Participants were recruited from an area called Kuri in Korea. A description of this site or information of the population from which the sample was drawn was not provided. Neuropsychological evaluation was not detailed enough neither was disease history of the control group assessed. Information on the type of fish consumed and methods of cooking were not included, all of which may have been relevant factors. Adjustment for confounding factors did not eliminate the possibility of residual confounding also influencing the findings. It was therefore difficult to rule out cognitive impairment or diseases that may affect cognitive function in the control subjects used for the study.

Tully (2003)

In 2003, Tully and colleagues (2003) published a paper in the British Journal of Nutrition that assessed the level of omega-3 PUFA among community dwellers living with Alzheimer's disease (AD). For the study, they recruited patients that attended clinic from the Mercer Institute for Research and Aging at St James Hospital, as part of a multi-factorial study on patients with Alzheimer's disease. The participants were all free living in the community and consisted of 119 females and 29 males of age range 49-92 years (Mean 76.5, SD 6.6) and mean clinical dementia rating (CDR) of 1(SD 0.62). The mean MMSE score was 19.5 (SD 4.8) with range 2-27. The control group was recruited from an active elderly retirement people who were free of cognitive impairment with mean MMSE score of 28.9 (SD 1.1) with range 25-30. The total people for the control were 45 (36 females and 9 males) aged 58-81 years (mean=70, SD=6.0). All participants had their medical history, brief neurological assessment, height, weight and blood pressure recorded. Those with history of stroke, hypertension, MMSE score <24, and on current warfarin therapy were excluded. Average storage period of serum samples was 2.54 years. Plasma cholesteryl ester-fatty acid composition was used as an established biomarker of n-3 PUFA and used to determine the n-3 PUFA status in each patient. Specific fatty acid levels were presented in g/100g total fatty acids. The fatty acid compositions for both patients and control were randomly analysed. All cases met criteria for NINCDS-ADRDA and ICD-10 criteria and involved neuropsychological testing and neuroimaging. This study suggested that low serum levels of cholesteryl ester-docosahexaenoic acid (DHA) levels was associated with Alzheimer's disease, with total saturated fatty acid levels and the cholesteryl ester-DHA as important determinants of MMSE score and Clinical dementia rating (CDR).

The analysis using ANOVA showed lower plasma levels of cholesteryl ester of linoleic acid and total n-6 PUFA ($p<0.005$) for the lowest quartile of MMSE score of patients compared with control. No significant lower levels were seen for other quartiles. Similarly, lower levels of plasma cholesteryl ester-EPA ($p<0.05$) and DHA ($p<0.001$) were observed in all MMSE score quartiles for those with AD patients compared to control. For the n-3 PUFA, the three highest MMSE score quartiles were different from controls ($p<0.001$), and patients with AD had lower levels of n-3 PUFA. The level of DHA was not significantly different in those with AD examined across age quartiles even though they were lower than the control. Findings from multiple regression showed that for CDR, based on the regression equation (r 0.429, $p=0.0008$), MMSE score was predicted by both cholesteryl ester-total saturated fatty acid levels (β 1.224, $p=0.0044$) and age (β 0.021, $p=0.0052$). Similarly, based on the regression equation (r 0.352, $p=0.0001$), MMSE score was predicted by cholesteryl ester-DHA (β 4.048, $P=0.001$) and cholesteryl ester-saturated fatty acid levels (β -7.48, $p=0.034$). However, age was not a significant determinant (β-0.101, $p=0.100$). The data analysis did not consider additional covariates apart from age. Therefore, it is likely that other important determinants like education and dietary habits could have been missed. The control subjects were reported to be younger than the cases. It is thus difficult to rule out the fact that it might have affected the results since increased age is associated with cognitive impairment or dementia.

Conquer (2000)

The study by Conquer *et al*. (2000) investigated the plasma fatty acid composition of various phospholipid fractions including total phospholipids (PL), phosphatidylcholine (PC), Phosphatidylethanolamine (PE), and lysophosphatidylcholine (lysoPC) of Alzheimer's disease (AD) patients and compared with those of elderly normal control subjects, other types of dementia (OD) and cognitive impairment (CIND). A total of 96 participants were selected for the study. Eighty-four of them (84), who were recruited from a large urban centre and screened for an ongoing longitudinal study, all donated blood samples for investigation. Each person had thorough physical examination, computed tomography (CT) scan and detailed neuropsychological assessment by a geriatrician. Others included haematology, renal, liver and metabolic function tests. The participants were classified into 4 groups namely; normal control group (19), AD group (19), OD (10) and CIND group (36). The AD group were diagnosed based on NINCD-ADRDA criteria for probable AD with decisions agreed jointly by a board- certified geriatrician and neuropsychologist. All individuals were screened to ensure they did not have alternative causes for dementia like chronic alcohol/drug abuse, chronic infections, stroke, hypoxia, metabolic disorders, nutritional disorders, intracranial mass lesions, psychoses, brain trauma and other neurological disease. The OD group, each person met criteria for DSM-IV, with the cause not due to AD. Eight of them had VaD based on DSM-IV criteria and vascular lesions detected by a CT scan. One had alcohol related dementia and another due to head trauma. In the CIND group (36) diagnosis was reached if a participant did not meet the DSM-IV criteria but scored less than the value for the age bracket from a neuropsychological examination. Fatty acid compositions were assessed in 4 different plasma lipids. Comparison of demographic characteristics among groups and fatty acid composition were analysed by ANOVA, followed by least square means if $P<0.05$. Analysis of covariance (ANCOVA) was done with adjustment for age and education, where $p<0.05$. Least squared means analysis was only done where $p<0.05$ from the ANCOVA. This study finding suggested that lower levels of n-3 fatty acids in the plasma of AD, OD and CIND individuals may be a risk factor for cognitive impairment and/ or dementia. The analysis using ANOVA showed that the levels of EPA (20; 5n-3), DHA, total n-3 fatty acids and the n-3/n-6 ratio for PL and PC were lower in the AD, OD and CIND groups than the control. Similarly, for plasma PE, the levels of EPA (20:5n-3), DHA, and the total n-3 fatty acid except n-3/n-6 ratio, were significantly lower in the AD, OD and the CIND groups. For the LysoPC fraction, there was no statistically significant difference in the fatty acid composition ($p>0.05$) except for DHA that was significantly lower only in the CIND group (0.1%) compared to AD (0.49%), OD (0.4%) and normal (0.48%). Plasma phospholipid 24:0 was lower in the AD, OD, and the CIND compared to normal group. Total n-6 fatty acid levels were lower in the AD and CIND groups only. The study considered age and education as important covariates in the statistical analysis using ANCOVA but further adjustments for confounding factors would have provided better insight on the relationships of the different fatty acid composition in the various plasma lipids and dementia. No information on dietary intake or histories were recorded on patients, meaning it is uncertain if patients currently consume or previously consumed diets lower in omega-3 fatty acids. Also, socioeconomic background may have played a role in dietary choices because patient groups were less educated than the control group, and education is a gross indicator of socioeconomic level.

4.3.1.3 Cohort studies

Barberger-Gateau (2002)

In 2002, Barberger-Gateau *et al.* (2002) published a short report in BMJ, suggesting that there was a non-significant association of incident dementia with fish or seafood eating, but not with meat consumption. They followed up 1674 participants who were aged 68 years and over from the 3rd wave survey of the PAQUID epidemiological study of cognitive and functional ageing without dementia and living at home in southwestern France. Each participant's food frequency consumption of meat and fish or seafood was recorded at baseline (1991-2) in four levels. The participants were re-examined in 2, 5 and 7 years afterward, and their dementia and AD status was diagnosed using MSE or DSM-III-R criteria with the neurologist's confirmation. In total 1416 participants were followed up at least one of the 3 follow-up visits (84.6%). There was a significant increase in the risk of dementia with lower level of fish or seafood consumption: the incidence of dementia was 1.00 per 100 person years in participants who ate fish/seafood "Once a day", 2.05 in those who ate "at least once a week but not every day", 2.90 in those "eating from time to time", and 6.61 in those "never eating". Such a trend was also found for incident AD. In an age-sex adjusted Cox regression model analysis, the authors found that participants who ate fish or seafood "at least once per week" had a reduced risk of incident dementia (HR 0.66, 95% CI 0.47-0.93) in comparison with those that consumed at the lower level, but not significantly reduced in the risk of AD (0.69, 0.47-1.01). After further adjustment for education (i.e. age, sex and educational level), the reduced risk of incident dementia was not significant (0.73, 0.52-1.03). The authors analysed the data of meat consumption and found no significant association with the risk of incident dementia (age and sex adjusted HR 0.56, 0.26-1.20). The data of AD in relation to meat was not presented in the paper. Although the cohort was well followed up, the baseline measurement of fish consumption was mixed with other seafood consumptions, and the association between high consumption of fish and reduced risk of dementia was not ensured from more confounding adjustment, which was missed in the current short report, for example, smoking. In 2 years later, Barberger-Gateau *et al.* (2002) published a full paper of "Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort" in other journal (Larrieu *et al.,* 2004), including additional data on regular fish consumers that was omitted previously in the same data of "fish, meat, and risk of dementia: cohort study". They reported that the age-sex-education adjusted RR for AD in participants who ate fish or seafood regularly was 0.77 (0.52-1.14) in comparison with those consumed at the lower level, but the RR figure for incident dementia of 0.66 (0.46-0.92) (Larrieu *et al.,* 2004) was similar to that in the earlier paper 0.66 (0.47-0.93) (Barberger-Gateau *et al.*, 2002).

Barberger-Gateau (2007)

Barberger-Gateau *et al.* (2007) showed a reduction in the risk of dementia and AD among frequent consumers of fish, fruit and vegetables and omega-3 fatty acid, particularly among APOE 4 negative individual in the Three-City prospective cohort study of vascular risk factors for dementia. A sample of 9294 non-institutionalized participants aged ≥65years living in three cities (Bordeaux, Dijon, Montpellier) in France were recruited at baseline (1999-2000) and followed-up for four years (mean period of 3.48 years) (1999-2004). At baseline, the participants' dietary intake of meat and poultry, fish with seafood, eggs, milk, diary product, dietary fat, cereals with bread and starch, raw fruit and vegetable, pulses and cooked fruit or vegetable were examined using a short food frequency questionnaire subdivided into 6 consumption level. The participants' sociodemographic data were also documented at the preliminary stage of the study. Participants underwent three-step procedures to establish their dementia status. This involved the administration of battery of neuropsychological tests by an expert in psychology, after which a neurologist re-examined the participants to ascertain the diagnosis. An independent team of neurologists finally reviewed the diagnosis using the DSM-IV criteria for dementia and the NINCDS- ADRDA for AD. Over a follow-up period of 4 years, a sample of 8085 (89.1%) non-demented participants was examined at least once. A total of 281 dementia cases (144 at 2 years and 137 at 4 years follow up) emerged with 183 cases of AD within these periods. The result showed a non-significant reduction in the risk of dementia among two of the fish intake level of consumption (highest and lowest intake level) after adjusting for confounding variables. No relationship was found between the intake of corn oil, peanut oil, lard, meat, or wine and the risk of all cause dementia in an age adjusted univariate analysis ($p > 0.25$) hazard Ratio (HR) (not reported). Using a multivariate adjusted analysis model, a significant reduced risk of dementia was found among participants that consume fish 2-3 times a week HR 0.68 (0.48-0.98), 0.81 (0.57-1.17) among once/week fish consumers and 0.81 (0.45-1.46) among ≥4 times/week fish consumers, when sex, education, city, income, and marital status, were added into the adjusted model and compared with the never/<once/week fish consumers. Similar trend was also encountered for the risk of AD. Since fish intake, ApoE genotype and dementia risk had an interaction, when two of the three interaction terms were considered, the already adjusted model was stratified by ApoE, and the result showed a beneficial effect between the intake of fish and the risk of all cause dementia among only the ApoE non-carriers participants with (HR 0.53, 0.34-0.82) at 2-3 times/week fish consumption level, 0.66 (0.42-1.01) at fish intake level of once a week and 0.80 (0.41-1.58) at fish intake level of ≥4 times/week. After further adjustment for BMI and diabetes, there was a slight change in the result. A non-significant reduced risk of AD was found in two of the fish intake level of (≥4 times/week and once a week) when ApoE genotype was

introduced into the already adjusted model. There was a slight changed in HR for AD risk when the model was further adjusted with BMI and diabetes. A borderline significant reduction in the risk of dementia was realized among regular fish eaters of (at least once a week) with (HR 0.75, 0.54-1.04). When ApoE4 status was added into the adjusted model, a significant reduction in the risk of dementia was obvious only among the non-carriers of APOE4 (HR 0.60, 0.41-0.89), and with no significant association among the APOE4 carriers (HR 1.28, 0.58-2.83). The beneficial effect was maintained among the ApoE 4 negative, when further adjustment was made with BMI and diabetes (HR 0.60, 0.40-0.90). The same significant trend was maintained in the risk of AD among regular fish eaters after adjusting for APOE genotype, BMI, and diabetes (HR 0.65, 0.43-0.994). A 60% reduced risk of dementia was found among frequent omega 3 rich oils consumers after adjusting for confounders, but no significant reduction was found for intake of any other kind of dietary fat. The findings remained practically unaffected when APOE genotype, BMI and diabetes was introduced into the adjusted model. A reduced risk of all-cause dementia was also found among the participants that consumed fruit and vegetables (HR 0.72, 0.53-0.97) in a fully adjusted model.

This cohort study had enough years of follow up, but their preliminary fish consumption data collection was along with seafood and other types of foods. The study acknowledged that despite controlling for possible confounders, there might still be the presence of some residual confounders, which could have impacted on the findings.

Devore (2009)

Devore *et al.* (2009) investigated the association between dietary intake of fish and omega-3 polyunsaturated fatty acids (PUFA) in relation to long-term dementia risk. In the year 1990, 7983 (78%) eligible inhabitants of Ommoord aged 55 years or more were recruited at baseline based on agreement in the Rotterdam population-based Study. At the commencement of the study, health and lifestyle information were collected during the period of 1990-1993. This involved an extensive home interview and 2 clinical assessments of both male and female participants. 7046(88%) of the chosen cohort were checked incessantly throughout the mean follow up period of 9.6 years for death rate and disease state of participants. Cognitive screening was performed on all participants at baseline, and they were all confirmed free of dementia. 6444 participants were left after exclusion of 602 due to questionable cognitive status and bias in diet recall mainly because of living in nursing home. After further exclusion of 1049 participants were due to inconsistencies in dietary response, missing the last visit and not having a dietician available at the last visit. This reduced the final cohort to 5,395 participants that were dementia free and had complete dietary information for analysis. A 2-step protocol was employed to collect dietary intake data. This include: a meal-based check list to prompt recall of food that were previously consumed at least twice/month A validated 170 items semi-quantitative (SFFQ) was later employed to collect the frequency of fish intake from each participant by a trained dietitian. This frequency was recorded in times per day, week, or month. Total fish intake was assessed using 3 categories: (none, low and high); while the fish type was (none, lean and fatty fish). Total Omega-3 PUFA (EPA+DHA), and ALA, EPA, DHA was also calculated for each participant. A 3-step protocol was used at baseline for dementia diagnosis: These comprises of MMSE and Geriatric mental state (GMS) schedule. Those that present with MMSE scores of <26 or GMS scores >0 underwent the Camdex test, and suspected participants with dementia were further evaluated by a neurologist and neuropsychologist using neuroimaging data to identify brain abnormalities. Further monitoring of participants was done to establish any memory problem and dementia state using a computerized linkage of dataset and digitalized medical records. Lastly, the dementia diagnosis was confirmed using 3 experts' committee following the DSM-III-R criteria for dementia, NINCDS-ADRDA for AD, and NINDS-AIREN for vascular dementia. 465 new cases of dementia were developed over 9.6 years' follow-up period (with 365 AD cases).

Using an age-sex adjusted Cox hazard model, total fish consumption was not associated with long-term risk of dementia and AD. Participants with higher fish consumption level (29.6g/day) showed (HR 0.93, 95%CI 0.74-1.17) and 0.99 (0.77-1.29) in relation to the risk of dementia and AD respectively, when compared to never fish eaters over a longer period. Further adjustment with education, total energy intake, alcohol intake, smoking, BMI, high total cholesterol, baseline hypertension, intake of vitamin E, supplement use, history of stroke, myocardial infarction (MI) and type 2 diabetes, showed (HR 0.95, 0.76-1.19) for dementia and 0.99 (0.76-1.29 for AD when compared to never fish eaters. Participants with low fish consumption level (8.2g/day) in relation to dementia risk, showed (HR 0.91, 0.73-1.14) and 1.05(0.82-1.34) for AD when adjusted for age and sex. After further adjustment with potential confounders, the HR for dementia risk was 0.94 (0.75-1.17) and 1.07 (0.83-1.37) for AD, when compared to never eaters. When fish type (fatty fish) was considered and compared with never consumers of fish, similar (HR 0.98, 0.77-1.24) for risk of dementia was found, which was quite the same as the AD result (HR not reported). No relationship was found with increased intake of omega-3 PUFA and the risk of dementia and AD, despite using only age or multivariate adjusted model. The age-adjusted model for dementia risk showed (HR 0.93, 0.74-1.16) when the highest (3rd) tertile intake of omega-3 PUFA was compared with the lowest (1st) tertile omega-3 intake level, and (HR 0.90, 0.73-1.12) when the 2nd tertile omega-3 PUFA intake level was compared with the lowest tertile. No association was also found with dementia risk when higher tertile of long chain omega-3 PUFA was compared with lower tertile of omega-3 PUFA (HR 0.97, 0.77-1.21) in the multivariate adjusted model. The matched HR for AD was quite similar (1.05, 0.81-1.36).

This same trend of no relationship of dementia risk was also found when the highest tertile intake of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and alpha-linoleic acid (ALA) were considered independently (HR 0.97, 0.77-1.21) and 0.99 (0.79-1.24) (HR of ALA not reported), in comparison with lowest tertile in the multivariate adjusted models. The HR of 2nd tertile EPA and DHA intake level for risk of dementia, when compared with their lowest tertile intake level was 0.87 (0.70-1.08) and 0.91 (0.73-1.13) respectively (HR for ALA not reported). Further analysis was done by comparing shorter follow up years (0-8) with longer years (9-14). The follow up period of 0-8 years showed a non-significant reduced risk of Alzheimer's disease with higher fish and long chain omega-3 PUFA intake (HR 0.78, 0.53-1.16) and 0.76 (0.51-1.13) respectively, but no relationship was found over a period 9-14 years (HR 1.20, 0.85-1.72) for higher fish consumption and 1.16 (0.84-1.60) for highest omega-3 PUFA intake. The same trend was reported when EPA and DHA was considered separately. Similar trend was also reported for risk of dementia, but the HR result was not shown.

The large prospective design of this study with its longer follow-up as well as a significant number of dementia cases contributed immensely to the long-term risk estimates. This study considered varieties of confounding variables, but this did not substantially affect the result. The baseline dietary information data collected might not have shown a positive reflection of the food intake level of the participants over a longer period. Higher consumption of cod fish (lean) limited the ability of this study to specifically evaluate the association that fatty fish have with the risk of dementia.

Morris (2003)

Morris *et al.* (2003) acknowledged a reduction in the risk of AD after dietary consumption of fish and omega 3 polyunsaturated fatty acids (PUFA) in the Chicago Health and Aging population-based study of risk factors for AD. 8501 inhabitants aged ≥65 years were selected between 1993 and 1997 in the south-side Chicago, III, community census. Among this selected population, a total of 6158 (78.8% out of 7813 survivors) partook in an hour and a half interview that involves the 4 cognitive tests assessment. 65% of the population was classified as black, 38% as white, with a mean educational level of 11.8 years. Of the interviewed population, 1056 participants were chosen randomly from a sample stratified by age, sex, race, cognitive behaviour (good, intermediate, or poor) for clinical examination detect AD prevalence. From this population, 729 (76% of 961 survivors) were assessed. The preliminary stage of this study acknowledged 3838 cohorts with absence of AD (3352 with good cognitive performance and 486 with poor cognitive performance but no AD). A follow-up interview was conducted on 4320 participants (86.7% of 4983 survivors) that responded after the 3 years' baseline data collection. A total of 1249 participant were randomly chosen from this sample for clinical assessment to detect new AD cases through stratification by age, sex, race, decrease in cognitive behaviour (no, minor, major decrease). From this random selection, 842 (73.9% of 1140) individuals accepted to participate, but only 815 participants provided complete data for analysis. During a mean period of 1.9 years after the participants' preliminary assessment or 2.3 years before their clinical examination, their dietary intake was examined using a modified 154-questions with 139 items Harvard self-administered food frequency questionnaire (FFQ). This comprises of 4 seafood (shrimps/lobster, crabs, fresh fish, tuna fish sandwich, fish sticks/fish cakes/ fish sandwich) and other food items, among which are (meat product, vitamin supplement). The participants AD status was established using well organised neurologic clinical assessments that comprises of specialists' team of neurologist, phlebotomist, nurse, and neuropsychological technician. Following the expert's judgement, the participants' full medical history, laboratory examination, assessment of participant cognitive status through interview, medication use, neurological assessment, and neuropsychological status was investigated. Magnetic resonance imaging (MRI) was incorporated into the examination for only those participants that display signs of being demented or has undefined level of their stroke status. Using standardized diagnosis criteria of the National Institute of Neurological and Communicative Disorders, Stroke and Alzheimer's disease and Associated Disorders Association (NINCDS-ADADA) their AD status was established by a neurological expert blinded from the cohort food intake.

In an age adjusted logistic regression model, a non-significant reduced risk of AD was found in fish consumers of at least once/week (RR 0.5, 0.2-1.0), ≥twice/week (0.6, 0.2-1.4) and 1-3 times/month (0.7, 0.3-1.6) in comparison with never fish consumers. After further adjustment with sex, race, education, presence of APOE4, and total energy intake, a similar 60% significant reduced risk of AD was shown across two of the fish consumption level of once/week and ≥ twice/week with RR (0.4, 0.2-0.9), while a non-significant reduced risk of AD was still maintained at fish consumption level of 1-3times/month with RR (0.6, 0.3-1.3) despite the adjustment for confounders.

Furthermore, in a multivariate adjusted model (age included), a significant reduction in the risk of AD was found after intake of total omega-3 PUFA. This controlled for race, sex, age, total energy intake, APOE4 status, education, (race x APOE4 interaction), period of observation, indicator variables for fish consumption 1-3 times per month, once per week and 2 or more times a week. A 70% significant reduced risk of AD was found after adjusting for age, when the participants at the highest intake level of omega-3 PUFA (5th quintile) was compare to those at the lowest intake level (1st quintile) with RR (0.3, 0.1-0.7). The significant association was maintained with a minor change in the relative risk (0.4, 0.1-0.9) after further adjustment with probable confounders. Two of the total omega-3 PUFA intake levels (3rd and 4th quintile) showed a non-significant association with the risk of AD when fully adjusted with RR 0.6 (0.2-1.7) and 0.7 (0.3-1.6) respectively, while the 2nd quintile intake level showed a non-significant increased risk of AD with RR 1.2 (0.5-3.0) in comparison with the lowest quintile. More beneficial effect was found with the risk of AD when only the intake of docosahexaenoic acids (DHA) 22:6 n-3 was considered instead of the total omega-3 fatty acid intake with RR 0.3 (0.1-0.9) when the 5th highest quintile was compared with the 1st lowest quintile, after adjusting for all the possible confounding variables.

This study was able to establish the beneficial association that DHA have with AD risk, which eliminate the uncertainty of the result. The use of the random sampling technique for the participants' selection minimised the issue of bias in this study. Also, the investigators were unable to collect the dietary intake data at baseline from many of the participants. This could have affected the result, if the disease has already manifested when their diet was later evaluated during the research.

Schaefer (2006)

Schaefer *et al.* (2006) established a reduced risk of developing dementia and AD with plasma phosphatidylcholine (PC) docosahexaenoic acid (DHA) content in the Framingham Heart Study. During the period of 1986 to 1988, 1921 males and females' participants aged between 55 and 88 years who were living and free of dementia were recruited at the 20th biennial examination 14-15 cycles in the United State. 899 (74.4%) participants from the 1208 (62.9%) sample with at least one year of follow up that took part in the baseline examination, provided plasma sample for PC fatty acid assessment and this constituted the study population, out of which 488 participants (54.3%) provided dietary information. They all had a followed-up period of 16 years with an (average of 9.1years). Dietary fish and DHA intake were examined using a 126-item semi-quantitative food frequency questionnaire (FFQ). The participants were expected to have received and filled the questionaries before the 20th biennial examination. Total energy intake < 600 calories and >4200 calories excluded. Fish intake was estimated in servings/week. At baseline, this was 2.0 (2.0) for men and 2.1 (1.8) for women. The baseline plasma PC DHA levels was assessed using four quartiles. Mini-Mental State Examination (MMSE) was performed on each participant at every biennial examination. Those that scored less than the education-based cut-offs or had lost ≥ 3 points on the MMSE, further had a neurological and a neuropsychological investigation. A comprehensive case review by board of at least 2 neurologists and neuropsychologist were conducted for each dementia diagnosis. The dementia and AD diagnosis were determined using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria respectively. All established dementia cases after the 20th biennial examination were included, while the previously established cases were excluded from the analysis. 99 new cases of dementia occurred during a mean follow up of 9.1 years with (71 AD cases). In an age-sex adjusted Cox proportional hazards regression model, a significantly reduced risk of incident all-cause dementia was found among the participants in the plasma PC DHA highest quartile in comparison to those in the lowest quartile (RR 0.53, 0.29-0.98). Further adjustment with APOE allele, homocysteine concentration, and educational level, the RR was changed to 0.52 (0.26-1.04), making this non-significant.

However, when subjects with plasma PC DHA levels in the upper quartile were compared with all 3 lower quartiles combined, the RR was 0.53 (0.29-0.97) after adjustment.

A non-significant reduced risk of AD was found when the participants in the highest plasma PC DHA quartile level was compared with other 3 lower quartiles with a RR 0.60 (0.32-1.12), when age and sex was adjusted, 0.59 (0.31-1.14) when APOE allele was added into the adjusted model, and finally 0.61 (0.31-1.18) when plasma homocysteine concentration and educational level was further introduced into the already adjusted model. No substantial change in the results for both risks of dementia and AD was observed when BMI, hypertension, diabetes mellitus, smoking, alcohol intake, stroke history was later added to the already adjusted model (RR 0.54, 0.29-0.98) compared to 0.53 (0.29-0.97) for all dementia and 0.62 (0.32-1.22) compared to 0.61 (0.31-1.18) for AD. No significant relationship was found with all dementia and AD risk, with plasma PC level of linoleic acid, α-linolenic acid, eicosapentaenoic acid, palmitic acid, oleic acid, arachidonic acid, stearic acid in an age-sex adjusted model except with (RR 1.27, 1.01-1.61) for plasma PC level of linoleic acid in association with AD risk. The significant association changed when APOE, educational level and homocysteine was introduced into the adjusted model (RR 1.24, 0.97-1.59). A non-significant reduced risk of dementia and AD was found among participants at upper quartile dietary DHA intake level when compared to those at lower 3quartiles dietary intake level after adjusting for probable confounders (RR 0.56, 0.23-1.40) for dementia and 0.63 (0.23-1.72) for AD. In the participants that consumed fish for ≥twice/week when compared with those that consumed fish for at most twice/week, a non-significant reduction in the risk of dementia and AD was found with RR of 0.61 (0.28-1.33) and 0.50 (0.20-1.27) respectively. This cohort study had a long follow up period and is the first study to investigate the relationship of plasma PC DHA content with incident dementia and AD. The plasma PC DHA level was measured only once during the data collection period, and dietary data was only available for a subset of the sample which were non-randomly selected.

Lopez (2011)

In 2011, Lopez and colleagues (2011) published an article in the Journal of Nutrition, Health and Aging suggesting that Plasma and dietary DHA may protect against dementia, with fish intake exhibiting similar but non-significant effect. They recruited 402 community dwelling individuals who participated in two separate research visits at a clinic in both 1988-91 and 1991-93. All of them had their dietary DHA and fish consumption data recorded at the first visit in 1988-91. At the next visit in 1991-93, a total of 266 eligible male and female participants aged ≥65 years were selected and had their plasma DHA recorded. Only 242 had both dietary and fish consumption data. Cognitive function test and clinical examination were done by a psychometrics and neurologist followed by a computerised tomography brain scan two weeks later. Three exposure variables were considered, and they included plasma DHA, dietary DHA and consumption of dark meat fish. To adjust for skewed distribution, plasma and dietary DHA were log transformed and modelled as continuous, categorical (tertiles) and lowest tertile vs other tertiles. Fish intake was considered in the levels of rarely or never, 1-3 times per Month, 1 time per Week, 2-4 times per Week, 5-6 times per Week, daily and 2 times per day. All-dementia and AD cases (outcome variables) were diagnosed based on data of psychometrist cognitive function test, neurologist clinical examination, computer aided brain scan and NINICDS-ADRDA criteria. The findings from multivariate logistic regression after adjusting for age, sex, education, ApoE4 and history of stroke showed significant reduction of the odds for all cause dementia for the highest tertile in Plasma DHA (0.35 95% CI 0.17-0.92) and for AD (0.40 95% CI 0.15-1.10). The outcome for dietary DHA was similar, with the Odds significantly reduced for all-cause dementia (0.27 95%CI

0.09-0.79) and for AD (0.28 95% CI 0.09-0.93). The findings using continuous DHA showed non-significant reduction of the Odds for all cause dementia (OR 0.72, 0.49-1.05) and AD (OR 0.76, 0.50-1.14) in the plasma DHA. However, for higher dietary DHA (as per log SD increase), the Odds was significantly reduced for all-cause dementia (0.53, 95% CI 0.34-0.81) and AD (0.52, 0.32-0.84). On the contrary, the findings for the lower tertile when compared to the two highest tertiles showed significantly increased odds for all cause dementia (OR 2.35, 1.12-4.92) and AD (OR 2.33, 1.04-5.21) in the Plasma DHA. The Odds were even higher in the dietary DHA, for all-cause dementia (OR 4.31, 1.87-9.92) and AD (OR 3.43, 1.42-8.26). Further adjustments for Systolic B.P, smoking, alcohol, exercise, diabetes and BMI did not alter the associations in the analysis of the highest tertile or continuous data for plasma and dietary DHA. The odds did not substantially change in any of the analysis when carriers of the ApoE4 Allele gene were excluded. Fish consumption of at least one serving per week, had 49% reduced odds for all-cause dementia (95% CI 0.20-1.32) and 45% for AD (95% CI 0.20-1.48). However, the results were not significant, likely due to the relatively small number of participants eating at least one serving of fish per week (n=43) and due to the misclassification of annual food frequency questionnaires. It was also observed that fewer people (242) participated in the study of dietary intake of fish and dementia compared to those for plasma DHA (266) which formed basis for the report. The early part of the report suggested a case cohort design was used, but only the sample for plasma DHA analysis was taken once on the spot without any repeat, which was similar to a cross sectional design approach. Therefore, causality cannot be inferred from the findings.

Huangs (2005)

Huangs and colleagues (2005) demonstrated a reduction in the risk of dementia and AD with fatty fish intake, while lean fried fish had no beneficial effect especially with APOE4 non-carriers in the Cardiovascular Health Cognition Study (CHCS). At baseline, 5201 participants aged ≥ 65 years were randomly recruited between 1989 and 1990 from the Medicare eligibility list of four communities in the US (Forsyth County NC, Washington County MD, Sacramento CA, Pittsburgh PA) that were selected for the Cardiovascular Health Cognitive Study (CHCS). A total of 687 African American individuals were further recruited from three of the four communities (Forsyth, Sacramento, and Pittsburgh) two years after the preliminary recruitment between 1992 and 1993. 3602 participants that underwent brain MRI between 1992 and 1994 and have simultaneously completed the modified mini-mental state examination (3MSE) were examined in 1998 during the commencement of the CHCS study. Of these, 2,233 people were followed-up in 0.1-8.4 years with a mean of 5.4 years from the time the MRI examination was conducted and the start of AD, dementia or death. This study excluded all the participants that presented with prevalence of dementia (227) and mild cognitive impairment (MCI) (577). Additional 565 participants were eliminated due to insufficient data for fish intake/energy intake evaluation/ responses from extra 12 food items from the FFQ or extreme energy intake values. Additional variables that were collected at baseline, apart from dietary intakes, included education, age, gender, race, BMI and income. APOE genotype was assessed through DNA analysis from 91.5% of the participants. Various eating styles and habits, including fish consumption of each participant was assessed using a modified National Cancer Institute (NCI) 99-item FFQ with 46 extra questions on style and habit of food consumption. Fish consumption was assessed in four categories of number of servings per week which included; <0.25, 0.25-2, 2-4 and ≥4 for fatty fish (other fish and tuna). For lean fried fish, it included; <0.25, 0.25-2 and ≥2 servings per week. Participant's dementia status were diagnosed using the MMSE, and 3MSE at baseline (1989-1990) and afterward. Participants that were absence from the clinic were investigated via a Telephone Interview for Cognitive status

(TICS), while the Informant Questionnaire for Cognitive Decline in the Elderly (IQCoDE) was used to collect information from close relatives, GP, and caregivers of the deceased participants. All participants classified as high risk based on 80-point cut off on the 3MSE, a decline of at least 5 points on the 3MSE from previous examinations, a TICS score of <28, an IQCoDE score of >3.6, a stroke, a medical record review with a diagnosis of dementia, or residence in a nursing home), all participants at the Pittsburgh site and all minorities completed a neuropsychological test battery and were further assessed by neurologist if tests of memory or greater than one cognitive domain were failed (If refused / unable to attend clinic, or was deceased, dementia was assessed using the prospectively collected data from the annual clinic examination, enhanced with data from medical records, physician questionnaires, and informant/proxy interviews (including the Dementia Questionnaire). Finally, team of psychiatrists and neurologist certify the dementia status of participants' if there is presence of a progressive or static cognitive deficit severe enough to affect ADLs, an earlier normal level of intellectual functioning, impairment in ≥ 2 cognitive domains that does not necessarily consist of memory, and if the DSM-IV criteria were fulfilled. National Institute of Neurological and Communicative Disease and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria was used to ascertain AD status, and NINCDS-ADDTC was used for vascular dementia (VaD). Of the 2233 assessed participants, 378 had dementia, 190 AD, 50 had pure VaD. No significant difference was found in the incident of dementia or AD with greater servings of fried fish per week either before or after adjusting for fatty fish, age at baseline, minority status, gender, presence of APOE e4, energy, BMI, region, education, or income.

In a univariate analysis, the result shows a non-significant decrease in the incident of dementia (HR 0.75, 95% CI 0.55-1.03) and AD (HR 0.69, 0.45-1.06) when tuna or other non-fried fish was consumed once/month to twice/week in comparison to very low or non-consumption. Also, the consumption of tuna or other non-fried fish ≥ 4times /week, was significantly associated with protection against dementia (HR 0.63, 0.44-0.90)) and AD (HR 0.56, 0.34-0.91)).

However, these associations were not significantly affected after adjusting for age at baseline, sex, minority status, presence of APOEe4, energy, BMI, region, and fried fish intake (model 1), for consumption of tuna or other non-fried fish the HR for dementia was 0.65 (0.43-0.98) for ≥4times/week intake, 0.72 (0.51-1.02) for intake of 2-4 servings/week and 0.76 (0.55-1.06) for 0.25-2 servings/week when compared to <0.25 servings/week. For AD the HR was 0.54 (0.31-0.95) for consumption of tuna or other non-fried fish ≥4times /week, 0.59 (0.36-0.95) for 2-4 servings/week and 0.72 (0.46-1.12) for 0.25-2 servings/week when compared to <0.25 servings/week. After further adjustment with education and income (model 2) HRs were attenuated for consumption of tuna or other non-fried fish. HR for dementia was 0.79 (0.53-1.20) for ≥4times/week, 0.83 (0.59-1.18) for 2-4 servings/week and 0.85 (0.61-1.19) for 0.25-2 servings/week. For AD, HR was 0.69 (0.91-1.22) for ≥4times/week, 0.72 (0.44-1.17) for 2-4 servings/week and 0.85 (0.54-1.33) for 0.25-2 servings/week when compared to <0.25 servings/week. A non-significant reduced risk of dementia and AD with total fish consumption was attained with fully adjusted (HR 0.87, 0.62-1.23) for >1 servings/month to 2 servings/week of total fish consumption for dementia and 0.78 (0.48-1.28) for AD.

A non-significant increased risk of dementia (HR 1.11, 0.76-1.47) was found for intake of ≥2 servings/week of fried fish in (model 1) and 0.97 (0.69-1.35) in model 2 when compared with <0.25 servings/week, while (HR 1.18, 0.92-1.52) was found for consumption of 0.25-2 servings/week of fried fish in model 1 and (HR 1.12, 0.87-1.44) in model 2. For AD, a non-significant increased risk (HR 1.06, 0.66-1.69) was found for ≥2 servings/week of fried fish in (model 1) and 0.95 (0.60-1.52) in model 2, while (HR 1.07, 0.74-1.54) was found for 0.25-2 servings/week of fried fish in model 1 and (HR 0.97, 0.67-1.40) in model 2, when compared with <0.25 servings. HR of 2.6 (1.39-4.96) with increased risk of vascular dementia (VaD) was revealed after intake of 0.25-2 servings of fried fish/week but the (HR 1.68, 0.74-3.84) of fried fish intake level of 2-4 servings/week was not significantly associated with VaD. Similar findings were found after adjusting for confounding variables. The HR result for VaD risk in relation to fatty fish intake was like that of the risk of dementia but the findings was not reported. Findings from the analysis of dementia outcome and tuna or other fish stratified by APOE e4 status showed a small or no relationship among APOEe4 positive participants that consumed 2-4 servings/week of fatty fish (HR 0.91, 0.48-1.71), while the data from participants without APOEe4 showed a significantly lower HR of 0.60 (0.40-0.89) after consuming 2-4 servings/week of fatty fish. The HR was maintained for APOEe4 negative participants after controlling for confounders in model 1 but the association was attenuated in model 2. Adjusting for age, minority status, sex, APOE e4, energy, BMI, region, and fried fish in model 1 showed (HR 0.91, 0.44-1.88) among APOE e4 positive participants with ≥4 servings per week compared to < 0.25, and further adjustment using education and income (model 2) showed (HR 1.03, 0.49-2.16). The HRs for 2-4 servings/week were 0.99 (0.52-1.89) and 1.06 (0.55-2.05) for model 1 and model 2; and for 0.25-2 servings/week the HR was 1.07 (0.58-1.98) and 1.23 (0.66-2.30) for model 1 and 2 respectively. For APOEe4 negative participants that consumed ≥4 serving/ week of tuna or other fish, the HR for model 1 was 0.54 (0.31-0.95), HR for 2-4 servings of fish was 0.59 (0.36-0.95) and for 0.25-2 servings of fish the HR was 0.72 (0.46-1.12), compared to <0.25 servings/week. Further adjustment (model 2) showed (HR 0.69, 0.91-1.22) for ≥4 servings per week, (HR 0.72, 0.44-1.17) for 2-4 servings/week, and 0.85 (0.54-1.33) for 0.25-2 servings/week of tuna or other fish, compared to <0.25 servings/week.

A reasonable mean follow-up year was achieved in this cohort study with adjustment made with several probable confounders. This study reported that they are the first to establish the relationship of fish consumption with APOE4 allele's carrier and non-carrier. They mentioned that their baseline dietary assessment instrument was not with portion sizes, and the fish consumption frequency was restricted to 5 subdivisions.

I examined the quality of each of these studies and found that the quality of these articles was in general good (see Table 4.3).

Overall, the literature review showed that increased consumption of fish was probably associated with reduced risk of dementia and AD.

4.4 Discussion

In this study, a comprehensive systematic worldwide literature review was carried out to assess the association of fish consumption with dementia and AD risks in countries with different levels of income. The review revealed that most of the various studies summarised reported an inverse association of increased consumption of fish and the risk of dementia. This beneficial role of fish consumption on the risk of dementia is biologically plausible. This is ascribed to the presence of long chain omega-3 polyunsaturated fatty acids (PUFAs) as part of its constituents especially docosahexaenoic acid (DHA) (Uauy and Dangour, 2006; Connor and Connor, 2007) with anti-inflammatory, anti-atherosclerotic, anti-amyloid, antioxidant and anti-thrombotic properties (Calder, 2006; Innis, 2007). This protective effect of fish may be due to some other potential explanations. Increased consumption of fish could lower the risk of CVD through the vascular mechanism (Hu and Willett, 2002), and this could possibly reduce the risk of dementia. Fish is a nutritional source of high-quality animal protein and various essential nutrients, including vitamins, minerals and amino acids (Kawarazuka, 2010; Lund, 2013; FAO, 2018), which might have contributed to its effect in reducing the risk of dementia. Higher fish consumption may be attributed to reduced intake of saturated fat and it could also be ascribed to having a higher socio-economic status and having better dietary and healthy lifestyle. However, the notable variance in the findings of the studies in this systematic literature review could be ascribed to several methodological issues that make the analysis of epidemiological studies difficult. These issues could be explained by considering the specific type of fish consumed, duration of exposure to fish consumption, reverse causation (Protopathic bias), dosage of fish consumption, adjustments for confounders, genetic susceptibility, gender disparity in effect and different cooking techniques.

4.4.1 Type of fish consumed

The type of fish consumed might have influenced the findings of previous studies of fish consumption and the risk of dementia, since omega-3 PUFAs (particularly DHA) - a beneficial nutrient in fish is predominantly present in fatty fish. Huang *et al.* (2005) observed a 28% reduction in the risk of developing dementia after the intake of fatty fish, while no significant beneficial effect was found with the consumption of lean fried fish.

4.4.2 Duration of exposure to fish consumption

The beneficial effect of fish consumption may manifest over a shorter follow-up period as compared to a longer follow-up period. The Rotterdam population-based cohort study of 5386 participants aged ≥55 years found a significant reduction in the risk of developing dementia among >18.5g/day fish consumers (RR 0.4, 0.2-0.9) after a follow-up period of 2.1 years (Kalmijn *et al.*, 1997). However, no association of fish consumption was found with incidence dementia when the same cohort was followed up over a longer study period of 9.6 years (Devore *et al.*, 2009).

Similarly, a recently published Three-City cohort study of 5934 participants aged ≥65 years with 662 dementia cases also found no association of fish consumption with the risk of developing dementia and AD with HR 1.09 (0.72-1.67) and 1.06 (0.65-1.75) respectively, after a mean follow-up period of 9.8 years (Ngabirano *et al.*, 2019). The differences in the findings could be due to the changes in the participants' dietary intake including the consumption of fish over a longer period.

4.4.3 Reverse Causation (Protopathic bias)

The differences in findings between the short and long follow-up could also be due to reverse causation that materialises when there is behavioural modification due to underlying disease pathology (Ngabirano *et al.*, 2019), since the pathophysiology of dementia/AD start 10 to 20 years before the actual clinical manifestation of the disease (Amieva *et al.*, 2008; Braan *et al.*, 2011; Raskin *et al.*, 2015). It is difficult to ignore the possibility that the earlier dietary habits assessed before dementia manifestation was either affected or not by the gradual pathological process occurring in the affected individual. Therefore, it is difficult to conclude if the assessed dietary habit is influenced by the observed disease pathology. This was established in Wagner *et al.* (2018) study that demonstrated a decrease in the level of consumption of fish, fruits and vegetables in the years prior to dementia diagnosis.

4.4.4 Dosage of fish consumption

The quantity of fish consumed could have an impact on the dementia outcome. Morris *et al.* (2003) demonstrated a non-significant dose-response relationship of AD with fish consumption; RR 0.6 (0.3-1.3) in participants who consumed fish 1-3 times per month, 0.4 (0.2-0.9) in those who consumed fish once a week and 0.4 (0.2-0.9) in ≥ twice per week (trend p=0.07). However, non-significant associations of reduced risk of dementia were found with the highest level of fish consumption in other cohort studies (Barberger-Gateau *et al.*, 2002; Barberger-Gateau *et al.*, 2007; Schaefer *et al.*, 2006). This may be due to the small number of participants in these groups.

4.4.5 Adjustment for confounders

The heterogeneity in the relationship could be due to the inconsistency in controlling for potential confounders in the included studies. Some of the included studies only adjusted for age, sex and education (Barberger-Gateau *et al.*, 2002), while other studies additionally adjusted for health variables such as BMI, diabetes, hypertension and stroke that could confound the result or affect the association. However, most of the studies did not adjust for APOE- e4 allele, which is an important genetic factor that could impact on the association of fish consumption and dementia risk as evidenced in both Huang *et al.* (2005) and Barberger-Gateau *et al.* (2007).

4.4.6 Genetic susceptibility

The beneficial effect of fish consumption on incidence dementia may be influenced or attenuated by genetic susceptibility. Genetics play a huge role in neurodegenerative changes (Stern, 2012). This genetic factor comprises of a component called apolipoprotein E (APOE) allele. This APOE-e4 polymorphisms do impact on the response of lipid profile to fats consumption (Vincent *et al.*, 2002; Couture *et al.*, 2003), thus indicating the possibility of a differing response to omega-3 PUFA in fish. Apolipoprotein (APOE-e4) genotype allele carriers are susceptible to an increased risk of developing both the familial and the sporadic forms of dementia (Ashford, 2004; Qiu, Kivipelto and von Strauss, 2009; Seripa *et al.*, 2009). However, few of the included studies found a preventive effect of fish consumption among participants that are non-carriers of the APOE-e4 allele, but increased risk among the carriers of APOE-e4 allele (Huang *et al.*, 2005; Barberger-Gateau *et al.*, 2007).

4.4.7 Gender disparity in effect

Despite the significance of gender, minimal emphasis is put on the impact of gender differences on the association of fish consumption with the risk of incident dementia. In this review, most of the existing studies did not assess gender differences in their analysis. One recent study published in (2019) on the association of meat, fish, fruits and vegetables on the risk of long-term dementia and AD reported gender differences on meat and vegetable consumption on dementia risk but failed to report the gender differences on the association of fish consumption with dementia risk (Ngabirano *et al.,* 2019). In view of these findings and limited studies, more research is required to examine the impact of gender difference on the association of fish consumption and the risk of incident dementia.

4.4.8 Different cooking techniques

The variation in the results could also be attributed to the different cooking techniques, since fish is popularly deep-fried in the Western regions while grilling and steaming are popular in the Asian regions. This deep-frying could negatively impact on the protective effects of the constituents in fish through trans-fatty acids production and inflammation induction, which are two major causes of chronic diseases.

Other heterogeneity in findings could be attributed to variance in peoples' fish consumption and omega-3 fatty acid metabolism, variance in people's omega-3 fatty acid levels; that is the consumption of same amount of fish does not necessarily mean similar level of omega-3 fatty acid will be displayed due to different consumption of seafood and other omega-3 fatty acid containing foods. In addition, the discrepancy in findings could be due to using food frequency questionnaire in assessing the level of fish consumption, which might not certainly demonstrate the exact amounts of omega-3 fatty acid accrued after the consumption of fish. Information bias and random error in reporting of dietary exposure to fish consumption could also have caused the inconsistency in the findings. This could be due to the likelihood of over and underreporting of dietary exposure to fish consumption by people already living with dementia, therefore causing an underestimation of the true effect of the association, hence resulting in differential misclassification (van Staveren *et al.*, 1994). The possibility of residual confounders cannot be ruled out in addition to the sample size, selection bias and measures of dementia.

4.5 Conclusion

In summary, our systematic worldwide literature review suggests that higher fish consumption is associated with reduced risk of dementia and AD. Therefore, increased habitual consumption of fish throughout the life course may be preventative against the risk of dementia.

Table 4.1: Characteristics and findings of cross-sectional studies identified for the systematic literature review of the association of fish consumption and dementia risk

First Author; Publication year; Study type; Study location	Participants' characteristics; recruitment strategy Ethinicity	Sample size	Baseline measure of frequency of fish consumption; categories of comparison	Endpoint outcomes: Number of dementia cases; diagnosis criteria	Data analysis method: confounders adjusted	Findings
Albanese (2009): Cross-sectional study Latin America, China and India	Age ≥65 years. Recruited by door knocking between Jan 2003 and Nov 2007 from 11 sites across Peru, Mexico, China and India, Cuba, Dominican Republic and Venezuela. Ethnicity- NR	Total 14,956: Cuba 2,934; Dominican Rep 1,999; Peru 1927; Venezuela 1,939; Mexico 1,997; China 2,162; India 1,998.	Standardised questionnaires from 10/66 protocol using face-to-face interviews. Never; some days; most days; and every day. The fish intakes of "most days" and "every day" were combined as one category.	1,345 prevalent dementia cases: Cuba 316 Dominican Republic 235 Peru 165 Venezuela 140 Mexico 171 China 137 India 181 Dementia was assessed by 10/66 diagnostic algorithm.	PR estimated using Poisson regression. Adjustment for age, sex, educational level and family history of dementia, self-reported chronic diseases (stroke, diabetes, and CHD), ICD-10 depression, smoking habits, living arrangements and number of assets, daily intake of fruits/ vegetables, meat intake, and alcohol intake.	PR_{adj} (95% CIs) of dementia for each increase in fish consumption category: Cuba 0.81 (0.65-1.02) Dominican Rep 0.80 (0.65-1.00) Peru 0.76 (0.56-1.05) Venezuela 0.87 (0.56-1.34) Mexico 0.81 (0.62-1.08) China 0.58 (0.39-0.85) India 1.47 (0.92-2.35)

Conquer (2000): Case control Canada	Aged 77.5-83.3 years. Recruited 96 eligible participants from a large urban center. Ethnicity-NR	84 gave blood samples.	GLC analyzed fatty acid methyl esters in blood plasma. Fatty acids composition: EPA (20:5n-3), 24:0, DHA (22:6 n-3), total n-3 fatty acids, and n-3/n-6 ratio was assessed in 4 different fractions of plasma lipids [total phospholipid (PL), phosphatidylcholine (PC), phosphatidylethanolamine (PE), and lysophosphatidylcholine (lysoPC)].	29 cases (19 AD, 10 other dementia [OD]); 36 CIND; 19 controls. CT scan, Neuropsychological assessment performed by a geriatrician Diagnosis made using NINCD-ADRDA criteria and DSM-IV criteria.	ANOVA and ANCOVA used to estimate the multifactorial data of the fatty acid composition. Adjustment for age and education	In plasma PL and PC, the levels of EPA, DHA, total n-3 fatty acids and the n-3/n-6 ratio were lower in the AD, OD and CIND groups compared to the control group. In plasma PE, the levels of EPA, DHA, and the total n-3 fatty acid except n-3/n-6 ratio, were significantly lower in the AD, OD and the CIND groups. Plasma PL (24:0) was lower in the AD, OD, and the CIND compared to normal group. Total n-6 fatty acid levels were lower in the AD and CIND groups only. ($p \leq 0.05$; effect sizes not given)

Kim 2010: Case-control study Korea	Age ≥ 65 years. Recruited from the Kuri Area between Dec 2008 and Jan 2009. Ethnicity-NR	57	FFQ GLC analyzed fatty acid methyl esters in blood samples. Erythrocyte fatty acid composition as biomarker of n-3 PUFA were categorized into tertiles.	33 cases; 24 controls. Dementia detected by Korean Mini-Mental Status Examination (MMSE-K; controls score > 21, cases score ≤ 21).	OR estimated using a logistic regression model. Adjustment for age, sex, height, and energy intake.	OR_{adj} (95% CIs) of dementia: Highest tertile 0.68 (0.12-3.77) Middle tertile 0.53 (0.09-3.18) Lowest tertile REF.
Tully 2003: Case control study Ireland	Cases recruited from community dwellers registered with Mercer Institute for Research and Aging aged 49-92 years; mean CDR of 1 (SD 0.62) and	193	GLC analyzed fatty acid methyl esters of cholesteryl esters in blood plasma. Plasma cholesteryl ester-fatty acid composition as	148 cases (108 probable AD, 16 possible AD, 13 mixed AD and 11 vascular dementia); 45 controls. Screening with MMSE (controls score ≥24, cases score <24);	ANOVA was used to describe differences between cases and controls. Step-wise multiple regression analysis used to ascertain relative importance of age, sex and fatty acid	Cases had significant lower levels (p<0.001) of n-3 PUFA compared to control (effect size not given). Fatty acid levels predicted MMSE and CDR scores independently of age and sex.

mean MMSE 19.5 (SD 4.8). Controls recruited from active elderly retirement group aged 53-81 years. Ethnicity-NR	biomarker of n-3 PUFA.	Neuropsychological examination and neuroimaging. Diagnosis made using NINCDS-ADRDA and ICD-10 criteria.	composition on MMSE scores. .

Abbreviations: AD Diagnostic and treatment Center criteria -ADDTC; Alzheimer's-Disease-AD; Apolipoprotein E-APOE-e4; Analysis of Covariance-ANCOVA; Analysis of Variance-ANOVA; Blood Pressure-BP; Body Mass Index-BMI; Cambridge Mental Disorders of the Elderly Examination-CAMDEX; Cognitively Impaired No Dementia-CIND; Clinical Dementia Rating-CDR; Coronary Heart Disease-CHD; 95% Confidence Interval-95%CI; Computerised Tomography-CT; Diagnostic and Statistical Manual of Mental Disorders-III-Revised-DSM-III-R; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-DSM-IV; Docosahexaenoic acid-DHA; Eicosapentaenoic acid-EPA; Food-frequency questionnaire-FFQ; Gas Liquid Chromatography-GLC; Geriatric Mental State schedule-GMS; Hazard Ratio-HR; Informant Questionnaire for Cognitive Decline in the Elderly-IQCoDE; International Classification of Diseases, 10th revision-ICD-10; Lysophosphatidylcholine-lysoPC; Magnetic Resonance Imaging-MRI; Mini-Mental State Examination-MMSE; Myocardial Infarction-MI; omega-3 Poly-unsaturated fatty acids- n-3PUFA; National Institute of Neurological and Communicative Diseases and Stroke AD and Related Disorders Association-NINCDS-ADRDA; National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences NINDS-AIREN; Not reported-NR; Other dementia-OD; Odd Ratio-OR; Plasma phosphatidylcholine-PC; Phosphatidylethanolamine-PE; Prevalence ratio-PR; Relative Risk-RR; Semi-quantitative food-frequency questionnaire -SFFQ; Telephone Interview for Cognitive Status-TICS; Total phospholipid-PL; Vascular Dementia- VaD.

Table 4.2: Characteristics and findings of cohort studies identified for the systematic literature review of the association of fish consumption and dementia risk

First Author; Publication year; Study type (Study name); Study location	Participant characteristics at baseline and recruitment strategy Ethnicity	Sample size at follow up (% of baseline sample); Study duration	Baseline measure of fish consumption; Categories of frequency	Number of new dementia cases; Dementia diagnosis criteria	Data analysis; Adjustment for confounders	Findings
Barberger-Gateau (2007): Cohort study (Three-City) France	9,471 eligible community dwellers aged ≥65 years were recruited at baseline between 1999 and 2000. Ethnicity-NR	8,085 participants (85.4%) were followed up at least once over a mean period of 3.48 years.	A short FFQ. Daily; 4-6 times a week; 2-3 times weekly; once a week; less than once a week; and never.	281 (including 183 AD). Psychological and neurological examination and reassessment by neurologist was performed using the DSM-IV and NINCDS-ADRDA criteria.	HR estimated using a proportional hazard model with delayed entry. Adjustment for age, sex, education, city, income, marital status. Analysis of AD additionally adjusted for APOE-e4, BMI and diabetes.	HR_{adj} (95% CI) dementia: ≥4 times/week 0.81 (0.45-1.46) 2-3 times/week 0.68 (0.48-0.98) Once/week 0.81 (0.57-1.17) Never or <1/week REF HR_{adj} (95% CI) AD: ≥4 times/week 0.58 (0.25-1.34) 2-3 times/week 0.59 (0.37-0.94) Once/week 0.74 (0.46-1.17) Never or <1/week REF

						HR_{adj} (95% CI) dementia in APOE-e4 non-carriers: ≥ 4 times/week 0.78 (0.39-1.58) 2-3 times/week 0.54 (0.35-0.85) once /week 0.64 (0.41-1.00) Never or <1/week REF HR_{adj} (95%CI) dementia in APOE-e4 carriers: ≥4 times/week 0.36 (0.04-2.91) 2-3 times/week 1.24 (0.53-2.90) once/week 1.66 (0.72-3.83). Never or <1/week REF
Barberger-Gateau (2002): Cohort study (Personnes Agees QUID [PAQUID]) France*	1,674 eligible community dwellers aged ≥68 years were visited during the 3rd wave of the study between 1991 and 1992. Ethnicity-NR	1,416 participants (84.6%) took part in at least one of the follow up visits after 2, 5 and 7 years.	FFQ. Daily; at least once weekly (but not every day); from time to time (but not every week); never.	170 (including 135 AD). Screening with MMSE (decline ≥3 points from previous visit) and review using DSM-III-R with further	HR estimated using a Cox proportional hazard model with delayed entry. Adjustment for age, sex and education (at least primary school diploma vs less education).	HR_{adj} (95% CI) of dementia ≥once/week 0.73 (0.52-1.03) <once/week REF

				confirmation by a neurologist.		
Larrieu (2004b) *	The same as above	The same as above	Once a week or more; less than once a week		RR estimated using a Cox proportional hazard model with delayed entry. Adjustment for age, sex and education (at least primary school diploma vs less education).	RR_{adj} (95% CI) AD ≥once/week 0.77 (0.52-1.14) <once/week REF
Devore (2009): Cohort study (Rotterdam) Netherlands	7,983 community dwellers aged ≥55 years were recruited at baseline in 1990 (78% of eligible sample). Ethnicity-NR	5,395 participants (67.6%) were followed up over a mean period of 9.6 years.	A meal-based check list to inform semi-quantitative SFFQ. Times per day, week, or month (categorized as none, low [8.2g/day] and	465 (including 365 AD). Screening with MMSE <26 or GMS scores >0; CAMDEX and evaluation by a neurologist and neuropsychologist with neuroimaging and computerized	HR estimated using Cox proportional hazard models. Adjustment for age, sex, education, total energy intake, alcohol intake, smoking, BMI, high total cholesterol, baseline hypertension,	HR_{adj} (95% CI) dementia: High 0.95 (0.76-1.19) Low 0.94 (0.75-1.17) None REF HR_{adj} (95% CI) AD: High 0.99 (0.76-1.29) Low 1.07 (0.83-1.37) None REF

			high [29.6g/day]). Fish type was classified as “no”, “lean” and “fatty fish”.	linkage of dataset and digitalized medical records. Diagnosis made using DSM-III-R NINCDS-ADRDA and NINDS-AIREN criteria.	intake of vitamin E, supplement use, history of stroke, Myocardial infarction (MI) and type 2 diabetes.	
Huang (2005): Cohort study (Cardiovascular Health Cognitive Study [CHCS]) USA	2,798 eligible participants aged ≥65 years recruited between 1989 and 1994 from a randomised Medicare eligibility lists. Ethnicity-African Americans	2,233 (79.8%) participants were followed-up between 0.1-8.4 years (mean 5.4 years).	A modified National Cancer Institute FFQ Tuna and other fish: <0.25; 0.25-2; 2-4; ≥4 servings per week. Fried fish: <0.25; 0.25-2;	378 (including 190 AD and 50 VaD). 80-point cutoff and/or decline of ≥5 points on the 3MSE, TICS score < 28, IQCoDE score >3.6. Further assessment was performed by a neurologist using	HR estimated using Cox proportional hazard regression models. Adjustment for baseline age, minority status, gender, APOE-e4, energy intake, baseline BMI and region, education and income.	Tuna and other fish HR_{adj} (95% CI) dementia: ≥4/week 0.79 (0.53-1.20) 2-4/week 0.83 (0.59-1.18) 0.25-2/week 0.85 (0.61-1.19) <0.25/week REF HR_{adj} (95% CI) AD: ≥4/week 0.69(0.91-1.22) 2-4/week 0.72(0.44-1.17)

			≥2 servings per week.	DSM-IV, NINCDS-ADRDA and ADDTC criteria.		0.25-2/week 0.85 (0.54-1.33) <0.25/week REF Fried fish: HR_{adj} (95% CI) dementia: ≥2/week 0.97 (0.69-1.35) 0.25-2/week 1.12 (0.87-1.44) <0.25/week REF HR_{adj} (95% CI) AD: ≥2/week 0.95 (0.60-1.52) 0.25-2/week 0.97 (0.67-1.40) <0.25/week REF
Lopez (2011): Case-Cohort study (Rancho Bernardo) USA	1692 community dwellers aged ≥55 years participated in a clinic research visit in 1988-91. Of the 1349 participants aged ≥ 65 years, available between	242 (90.9%) participants who had data for dietary DHA and fish consumption were followed up for	SFFQ Rarely or never; 1-3 times/month; 1 time/week; 2-4	42 (including 30 AD). Screening with MMSE, neuropsychologic	OR estimated using a logistic regression model. Adjustment for age, sex, education,	OR_{adj} (95% CI) all-cause dementia: ≥1 serving/week 0.51 (0.20-1.32). REF (not specified)

	1991-93, 402 partook in all the clinic visits. Ethnicity-NR	approximately 3 years.	times per week; 5-6 times per week; daily and 2 times/day.	al test battery by a psychometrist and neurologist and CT examination. Diagnosis made using NINCDS-ADRDA criteria.	APOE-e4 status, stroke, systolic B.P, smoking, alcohol intake, exercise, diabetes and BMI.	OR_{adj} (95% CI) AD: ≥1 serving/week 0.55 (0.20-1.48). REF (not specified)
Morris (2003): Cohort study (Chicago Health and Aging Project [CHAP]) USA	6,158 participants aged ≥65 years recruited at baseline identified from that 1993-1997 south-side Chicago census programme (78.8% of eligible sample). 1140 randomly selected from survivors at follow-up. Ethnicity-Black 62% and White 38% Americans	815 participants (71.5%) were followed up over a mean period of 3.9 years.	FFQ. Never; 1-3 times/month; once/week; ≥ twice/week. .	131 cases of AD. Assessment by neuropsychological technician, nurse practitioner, phlebotomist and neurologist using the NINCDS-ADRDA criteria.	OR as estimates of RR estimated using a logistic regression model. Adjustment for race, sex, age, total energy intake, APOE-e4 status, education, race*APOE-e4 interaction, period of observation, and indicator variables for fish	RR_{adj} (95% CI) AD: ≥ twice/week 0.4 (0.2-0.9) once/week 0.4 (0.2-0.9) 1-3 times/month 0.6 (0.3-1.3) Never REF

					consumption levels.	
Schaefer (2006): Cohort study (Framingham Heart Study) USA	1,208 participants aged 55-88 years examined at the 20th biennial examination cycle 1986/1988 (62.9% of eligible sample). 899 selected based upon availability of plasma sample. Ethnicity-NR	488 participants who provided dietary information (54.3%) were followed up over a period of 16 years (mean 9.1 years).	A semi-quantitative SFFQ. >twice/week; ≤twice/week.	99 (including 71 AD). Screening with MMSE (score less than education-based cut-offs or lost ≥3 points) with neurological and neuropsychological examination using DSM-IV and NINCDS-ADRDA criteria.	RR estimated using a Cox proportional hazards regression analysis. Adjustment for age, sex, APOE-e4, homocysteine concentration, educational level, BMI, hypertension, diabetes mellitus, smoking status, alcohol intake, history of stroke, daily calorie intake.	HR_{adj} (95% CI) Dementia: >twice/week 0.61 (0.28-1.33) ≤twice/week REF HR_{adj} (95% CI) AD: >twice/week 0.50 (0.20-1.27) ≤twice/week REF
Fischer (2018): Cohort study (Aging, Cognition and Dementia in Primary Care	10,850 eligible participants aged ≥75 years recruited at baseline between January 2003 and November 2004. Of these 6619 were randomly chosen to	2,622 participants were followed up over a period of 10 years	A brief cognitive health food intake screener Never; <once/ week; once/week; several	418 cases of AD Screening by SIDAM and CERAD, Diagnosis by interviewer consensus; geriatrician or	HR estimated using a Joint Modeling that combines Cox proportional hazards sub-model and a linear-mixed-effects repeated-	HR_{adj} (95% CI) AD: Higher intake 0.98 (0.87- 1.11) REF (not specified)

Patients [AgeCoDe]) Germany	participate and 3327 were finally investigated. Ethnicity-NR		times/weeks; each day	geriatric psychologist using DSM-IV, ICD-10, NINCDS-ADRDA and NINDS-AIREN criteria	measures sub-model Adjustment for age, sex, BMI, education, and APOE-e4 status, smoking status and physical activity, depression, hypercholesterolemia, and a modified CCI score	
Ngabirano (2019): Cohort study (Three-City) France	9,294 eligible participants aged ≥65 years were recruited at baseline between 1999 and 2001. Ethnicity-NR	5,934 participants were followed up at least once over a mean period of 9.8 years	A short FFQ. Never; ≤1 time/week; ≈ 1 time/week; 2-3 times/week; 4-6 times/week, and daily.	662 (including 466 AD). Psychological and neurological examination and reassessment by neurologist was performed using the DSM-IV and NINCDS-ADRDA criteria.	HR estimated using a proportional hazard model with delayed entry. Adjustment for inclusion Centre sex, education, income, marital status, APOE-e4, smoking, alcohol consumption, physical activity four other food categories, energy intake, BMI,	HR_{adj} (95% CI) dementia: ≥4 times/week 1.09 (0.72–1.67) 2-3 times/week 1.20 (0.91–1.58) ≈ 1 time/week 1.14 (0.86–1.50) Never or <1/week REF HR_{adj} (95% CI) AD: ≥4 times/week 1.06 [0.65–1.75] 2-3 times/week 1.13 (0.82–1.55) ≈ 1 time/week 1.09 (0.79–1.50)

					diabetes, hypertension, hypercholesterolemia and depression	Never or <1/week REF
Tsurumaki (2019): Cohort study (Ohsaki) Japan	31,694 participants aged ≥65 years were recruited at baseline in December 2006. Of these 23,091 responded to a baseline questionnaire Ethnicity-NR	13,102 (99.1%) participants who provided dietary information were followed up over a period of 5.7 years	FFQ Almost never; 1-2 times/month; 1-2 times/week; 3-4 times/week; and almost every day. Daily intake later grouped into Quartile: Q1, Q2, Q3, and Q4	1,118 dementia cases	HR estimated using a Cox proportional hazards model Adjustment for age, sex, education level, BMI, stroke, hypertension, myocardial infarction, diabetes and hyperlipidemia, smoking, alcohol drinking, time spent walking, sleep duration, psychological distress score, cognitive function score, fruits, green and yellow vegetables.	HR_{adj} (95% CI) dementia: Q4 0.84 (0.71, 0.997) Q3 0.85 (0.73, 0.99) Q2 0.90 (0.74, 1.11) Q1 REF

Abbreviations: AD Diagnostic and treatment Center criteria -ADDTC; Alzheimer's Disease-AD; Apolipoprotein E-APOE-e4; Analysis of Covariance-ANCOVA; Analysis of Variance-ANOVA; Blood Pressure-BP; Body Mass Index-BMI; Cambridge Mental Disorders of the Elderly Examination-CAMDEX; Cognitively Impaired No Dementia-CIND; Clinical Dementia Rating-CDR; Coronary Heart Disease-CHD; 95% Confidence Interval-95%CI; Diagnostic and Statistical Manual of Mental Disorders-III-Revised-DSM-III-R; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-DSM-IV; Docosahexaenoic acid-DHA; Eicosapentaenoic acid-EPA; Food-frequency questionnaire-FFQ; Gas Liquid Chromatography-GLC; Geriatric Mental State schedule-GMS; Hazard Ratio-HR; Informant Questionnaire for Cognitive Decline in the Elderly-IQCoDE; International Classification of Diseases, 10th revision-ICD-10; Lysophosphatidylcholine-lysoPC; Magnetic Resonance Imaging-MRI; Mini-Mental State Examination-MMSE; Modified Mini-Mental State Examination-3MSE; Myocardial Infarction-MI; omega 3 Poly-unsaturated fatty acids-n-3PUFA; National Institute of Neurological and Communicative Diseases and Stroke AD and Related Disorders Association-NINCDS-ADRDA; National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences NINDS-AIREN; Not reported-NR Other dementia-OD; Odd Ratio-OR; Plasma phosphatidylcholine-PC; Phosphatidylethanolamine-PE; Prevalence ratio-PR; Relative Risk-RR; Semi-quantitative food-frequency questionnaire -SFFQ; Structured interview for the diagnosis of dementia and Alzheimer type, multi-infarct dementia and dementia of other aetiology-SIDAM; Telephone Interview for Cognitive Status-TICS; Total phospholipid-PL; Vascular Dementia-VaD.

*These two papers report on the same studied population but have different findings for AD as the earlier study did not adjust for education in its estimate for AD. Thus, the earlier study was used for its estimate for all-cause dementia and the second study was used for its estimate for AD.

Table 4.3: Quality assessment for the 11 articles identified that studied the association between fish consumption and the risk of dementia.

Study	**1**	**2**	**3**	**4**	**5**	**6**	7	**8**	**9**	**10**
Albanese *et al*. 2009	★	★	★		★	★	★	★	★	★
Conquer *et al*. 2000	★	★	★	★	★			★	★	
Kim *et al*. 2010			★		★		★	★	★	★
Tully *et al*. 2003	★	★	★	★	★			★	★	
Barberger-Gateau *et al*. 2007	★	★	★	★	★	★	★	★	★	★
Barberger-Gateau *et al*. 2002	★	★		★	★	★		★		★
Devore *et al*. 2009	★	★	★	★	★	★	★	★	★	★
Huangs *et al*. 2005	★	★	★	★	★	★	★	★	★	★
Lopez et al 2011		★	★		★	★	★	★	★	★
Morris *et al*. 2003	★	★	★	★	★	★	★	★	★	★
Schaefer *et al*. 2006	★	★	★	★	★	★	★	★	★	★

Cross-sectional Studies

1– Aims/objectives of the study clear and study design appropriate for the stated aim(s)
2 –The sample size justified
3 – Sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation.
4 – Selection process likely to select subjects/participants that were representative of the target/reference population under investigation.
5 – The exposure and outcome variables measured correctly using instruments/ measurements that had been trialed, piloted or published previously.
6 – Data analysis controlled for age, sex and education
7 – Data analysis controlled for other confounders
8 –Findings interpreted well
9 – Weakness mentioned and explained clearly
10 – Paper written well

Cohort Study

1 – Cohort truly representative
2 – Controls derived from the same cohort
3 – Clear measurement of fish consumption at baseline
4 – Adequacy Follow-up duration (≥12 months)
5 – Reliable methods of dementia and AD diagnosis (ie, Quality of outcome)
6 – Cohort data analysis controlled for age, sex and educational level
7 – Cohort data analysis controlled for other confounders
8 – Findings interpreted well
9 – Weakness mentioned and explained clearly
10 – Paper written well
N/A = Not applicable

Case-Control Study

1 – Is the case definition adequate? (Yes, with independent validation)

2 – Representativeness of the cases

3 – Selection of controls (community controls)

4 – Definition of controls (No history of the disease)

5 – Clear measurement of fish consumption (clear records or structured interview and with same for both cases/controls)

6 – Data analysis controlled for age, sex and educational level

7 – Data analysis controlled for other confounders

8 – Findings interpreted well

9 – Weakness mentioned and explained clearly

10 – Paper written well

CHAPTER FIVE: DETERMINANTS OF FISH CONSUMPTION IN OLDER PEOPLE: A COMMUNITY-BASED COHORT STUDY

5.1 Introduction

Globally, fish consumption has contributed immensely to the health of the people by reducing their morbidities and mortality (FAO, 2016). Its consumption has been associated with a decreased risk of cardiovascular diseases (CVD) (Larsson and Orsini, 2011). Fish contains essential nutrients, including vitamins, minerals and amino acids (Kawarazuka, 2010; Lund, 2013; FAO, 2016), which makes it generally accepted as a vital component of a healthy and balanced diet (Yaktine and Nesheim, 2007). It is a significant source of animal protein that contains essential nutrients among which are long chain omega-3 polyunsaturated fatty acids (Connor, 2000), that assist in promoting the cognitive wellbeing of people (Kalmijn *et al.,* 2004; van Gelder *et al.*, 2007). Our recent study (Bakre *et al.,* 2018) showed that older people with increased consumption of fish had a reduced risk of dementia. Fish consumption in older age benefits late-life quality (Schiepers *et al.,* 2010) and reduces the risks of neurodegenerative disorders (Zhang *et al.,* 2016) and all-cause mortality (Yamagishi *et al.,* 2008; Zhang *et al.,* 1999). However, many older people reduce their fish consumption or do not eat fish at all. Existing literature (Can, Günlü and Can 2015; Grieger, Miller and Cobiac, 2012) shows that older people eat less fish than young and middle-age populations, but the reasons for this are unclear. Few studies have examined factors influencing the consumption of fish in older people, despite the world's population aging. Therefore, guided by Carlucci *et al.* (2015) conceptual framework, this study was conducted to examine the data from a population-based cohort to identify the determinants of fish consumption in older people which may help to increase fish consumption in the aging population.

5.2 Methods

5.2.1 Study Participants

The study population was derived from the Anhui cohort study. The methods of the Anhui cohort study have been described in Chapter 3 and previous publications (Chen *et al.,* 2014). In brief, we randomly recruited 1810 people over 65 years old who had lived more than five years in Yiming subdistrict of Hefei city in 2001 (Chen *et al.,* 2004, Chen *et al.,* 2012) and 1709 over 60 years old from all 16 villages in Tangdian district of Yingshang county in 2003 (Chen *et al.,* 2005). In total 3336 adults agreed to participate in the present study (response rate of 94.8%), of whom 1736 were living in urban and 1600 in rural area. They were interviewed by a trained survey team from the Anhui Medical University. Permission for interview and written informed consent were obtained from each participant. In about 5% of participants who could not provide informed consent, their nearest relative or carer were approached to provide assent to participation. The interview was conducted using the general health and risk factor record and the Geriatric Mental State (GMS) questionnaire (Wave 1) (Chen *et al.,* 2005, Chen *et al.,* 2004). Participants' socio-demographic characteristics that comprise of their educational attainment, occupational class, level of income, financial status over the last two years, lifestyle, social networks and support, histories of chronic diseases and risk factors were recorded. Participants' anthropometric data and blood pressure were also measured. Participants' dementia and depression status were diagnosed using the Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy (GMS-AGECAT) data (Chen *et al.,* 2004). At one year after baseline, the interview team re-examined 2806 surviving participants (Wave 2), using the same protocol as before (Chen *et al.,* 2008). In 2007-2009 (in 6 years after baseline survey), 1757 survivors were successfully re-interviewed (Wave 3) (Chen *et al.,* 2014) and information about their dietary intakes of rice, wheat flour, meat, fish, egg, fresh vegetable, fruit, chilli pepper, garlic, ginger and different types of vegetable oils were collected. Participants' frequency of fish intake in the past two years was recorded as (1) Never eat, (2) ≤Once a week, (3) >Once a week and < Daily, (4) Once a day, and (5) ≥ Twice a day.

5.3 Data Analysis

We examined distributions of baseline risk factors and health conditions among participants with different levels of fish consumption documented at Wave 3 survey by chi-squared test for categorical variables and one-way analysis of variance for continuous outcome variables. We employed binomial logistic regression models to examine the determinants of older people having any level of fish consumption versus those who stated they "never eat" fish over the past two years. We calculated the odds ratio (OR) and 95% confidence intervals of each baseline factor associated with the consumption of fish in a 6-year follow up. In the models, we adjusted for age and sex first, to compute the OR. We further examined those variables that were significant in the age-sex adjusted analysis, with multivariate adjustment including waist circumference and smoking at the baseline. Finally, we analysed the data of different levels of fish consumptions respectively versus those who reported they "never eat" fish in the multivariate adjusted logistic regression models to investigate any trend in the associations of baseline risk factors with consumption of fish. All data analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL).

5.4 Results

Of 1757 surviving participants, 1697 (96.6%) responded to the fish consumption questionnaire. The average age (SD) of participants was 71.8 (6.9) years and 53.8% were women. With respect to the past two years there were 390 (23.0%) participants who reported they "never eat" fish, 737

(43.4%) who consumed fish “once a week”, 457 (26.9%) “More than twice a week”, and 113 (6.7%) “≥once a day”. Table 5.1 shows characteristics of participants across different fish consumption categories. Participants with increased consumption of fish were significantly more likely to be younger (except for participants aged 60-64 years, who were from rural areas only), not smoking and urban living, and to have larger waist circumference, high levels of education, occupational class and income, no financial difficulty, and high satisfaction of life at baseline. High level of fish consumption was significantly associated with being currently married, less frequently visiting children/relatives/neighbours, having help available when needed, and having normal blood pressure/controlled hypertension, hypercholesterolemia, diabetes and heart disease, but not depression and dementia. There were no significant differences in drinking alcohol, contacting friends in the community and activity of daily living (ADL) score (0 - ≥5) across four groups of fish consumption.

Table 5.2 shows numbers and age-sex adjusted ORs and 95% CIs of having any level of fish consumption versus “never eat”. The patterns of distributions of these baseline risk factors between combining any levels of fish consumption and “never eat” were similar to those in Table 5.1. After adjustment for age and sex, significantly reduced odds of eating fish were found in older people with increased age (except for 60-64 years, which were from participants in rural areas), smoking, rural living, low levels of education, occupation and income, financial difficulties and low satisfaction of life at baseline. The reduced odds were also found in those who had never married or divorced, visited children or other relatives daily, and had undetected hypertension, depression or dementia. But older people classified as overweight (23-<26 kg/m^2) and/or having central obesity (waist circumference (WC) action levels 1 and 2), heart disease and hypercholesterolemia at baseline had an increased consumption of fish.

In the multivariate adjusted analysis (Table 5.3), the significantly reduced odds of having any levels of fish consumption were observed in older people with increased age, female gender, low socio-economic status, financial difficulties and low satisfaction of life, had never married or divorced, and had undetected hypertension, depression and dementia. Having central obesity and heart disease at baseline was significantly associated with increased fish consumption in the follow up.

Table 5.4 shows odds of fish consumption at "once a week", "more than twice a week" and "≥once a day" in relation to baseline risk factors, respectively. We found that there were similar patterns of ORs for these risk factors to those in their combinations (i.e. in any levels of fish consumption in Table 5.3). The findings in Table 5.4 revealed some trends in ORs across different levels of fish consumption. In the age group of ≥ 80 years, a significantly reduced OR of fish consumption at "once a week", "more than twice a week" and "≥once a day" was 0.46, 0.26 and 0.12, respectively. The matched figures in women were 0.85, 0.39 and 0.34, in rural areas 0.20, 0.05 and 0.01, in financial difficulties 0.44, 0.14 and 0.04; all significant. Other factors (e.g. low education, occupation and income, smoking) showed similar trends in ORs with reduced level of fish consumption, except for heart disease and dementia (Table 5.4).

5.5 Discussion

Our population-based cohort study in China demonstrated that within an older population increased age, female gender, smoking, living in rural areas, low levels of education, occupation and income, financial difficulties, low level of life satisfaction, being never married/divorced, and having undetected hypertension, depression and dementia were associated with reduced consumption of fish in late life. Older people who had central obesity or heart disease may have increased consumption of fish.

Prevalence of fish consumption in older people

Previous studies showed that compared to young people, older adults had a lower consumption of fish. In Turkey, Erdogan, Mol and Cosansu (2011) found that the proportion of people eating fish twice a week at ages 41-50 years, 51-60 years and ≥60 years was 26.5%, 25.6% and 23.2% respectively. In a USA study of 932 current seafood consumers aged 65 years and above, 18.0% of older people consumed seafood two or more times/week (Hicks, Pivarnik and McDermott, 2008). Our finding of 26.9% of older people consuming fish more than twice a week is therefore slightly higher than those in Turkey and USA, but less than reported in a cross-sectional study in France of 9280 participants aged ≥65 years, where 44.1% had an intake of fish 2-3 times a week (Barberger-Gateau *et al.*, 2005). Our results show that 43.4 % of the participants consumed fish once a week, while Barberger-Gateau *et al.* (2005) reported a 38.4% fish intake of once a week among their French participants. The Anhui cohort study showed that 6.7% of older people consumed fish ≥Once a day, while 6.3% daily or almost daily fish consumption was reported in Tanskanen *et al.* (2001) cross-sectional study of 3204 Finnish adults aged 25-64 years old. There is therefore variation in the amount of fish consumption in older people in different countries, probably due to income, culture and geographic place.

Factors influencing the consumption of fish in older people

Age and *Sex*

Our data of the Anhui cohort study shows that the odds of fish consumption decrease as age increases even within an older population. This is in accordance with an Australian cross-sectional study of 854 participants aged ≥51 years old, which found an (OR 1.82, 1.20-2.75) for having ≥½ serving of seafood per week among those aged 51-75 years when compared to those aged ≥76 years (Grieger, Miller and Cobiac, 2012). Larrieu *et al.* (2004) also reported infrequent fish consumption among older participants in a large population-based cross-sectional study of 9250 French older adults aged ≥65years. In a cross-sectional study of 127 randomly selected participants, Can, Günlü and Can (2015) found that the annual fish consumption level of young people is almost double that of the older people. In contrast, in a Norway cross-sectional study of 9407 participants aged 45-69 years, Trondsen *et al.* (2004) observed that increase in age was associated with increased odds of fish consumption. Also, in a Belgium cross-sectional study examining 429 participants mean aged 40.6 years (age range ≤25->55), Verbeke and Vackier's (2005) found an increase in fish consumption level as age increases. The main literature indicates an inequality in fish consumption in older adults, although there are some inconsistent findings.

The lower odds of fish consumption found among females in this study was consistent with the findings of some previous studies. A Nigerian cross-sectional study of 210 participants aged 21-70 years revealed a significant reduction in fish consumption level among the female participants (Anyanwu, 2014). In Norway, examining a cross-sectional study of 3144 participants aged 16-79 years, Johansson *et al.* (1998) found an increased daily intake of fish among their male participants. In Taiwan, Li *et al.* (2001) carried out a cross-sectional study of 1200 participants aged 14-71 years and found a significantly reduced odds of fish consumption (OR 0.71) among female participants. However, in a Turkish study, Can, Günlü and Can (2015) found that the females' yearly fish intake level was 1.19 kg more than the male participants' intake level. The differences among our Chinese study, and the three reported above (Johansson *et al.,* 1998; Li *et al.,* 2001; Anyanwu, 2014) in comparison with the Turkish study (Can, Günlü and Can, 2015) could be due to some cultural differences or because women are more likely to be financially incapacitated, thereby making fish products very expensive to purchase, which in turn may impact on their frequency of fish consumption.

Socioeconomic Status

There are a number of studies examining the association of *educational level* with the consumption of fish. In a US cross-sectional study of 1062 participants aged 18 to over 65 years, Hicks, Pivarnik and McDermott (2008) found an increase in the frequency of seafood intake of two or more times a week among participants with higher educational level. Grieger, Miller and Cobiac (2012) Australian cross-sectional study of 854 participants found an increase in fresh finfish and canned fish consumption level among older participants aged ≥51 years old with higher educational level. A French cross-sectional study showed an increase in frequency of fish consumption as educational level increases among participants aged ≥65years (Barberger-Gateau *et al.*, 2005). The studies conducted by Can, Günlü and Can (2015) and Anyanwu (2014) in Turkey and Nigeria showed that people with low educational level had low level of fish consumption, which were consistent with the findings of our Anhui cohort study in China. But some other studies (Verbeke, Vackier, 2005) did not show a significant association of educational level with fish consumption. Trondsen *et al.* (2004) did not observe any significant effect of educational level on fish consumption. In Turkey, Erdogan, Mol and Cosansu (2011) examined 972 participants aged 20 to over 60 years and found that 89.6% of uneducated or primary school level participants consume seafood, more than the high school and university degree level participants with 80.8% and 85.4% seafood consumption respectively. The variation in the findings of each of the studies could be due to cultural differences in motivations for fish consumption. Where populations are relatively wealthy, e.g. such as in the United States of America, fish consumption is a choice. In poorer countries, it might be about what is available, so it has less to do with education. Coastal areas may also have more access to fresh fish regardless of wealth.

There are also some investigations on the association of *occupational class* with the consumption of fish. In Taiwan, Li *et al.* (2001) demonstrated that odds of fish consumption were reduced among the participants who had blue collar occupations. Johansson *et al.* (1998) also established in their Norwegian cross-sectional study of 3144 participants aged 16-79 years that blue-collar workers had a reduced intake of very-long-chain omega-3 fatty acids, which is the main component of fish protein. Galobardes, Morabia and Bernstein (2001) in their community-based study found a reduced consumption of fish among participants with manual or lower occupational class. Our study also showed reduced odds among the peasant, manual laborers and those with no formal occupation. The group of low occupational class may have low levels of education and income. Both low levels of education and income appear to reduce the consumption of fish in the population throughout the life course including in older people.

With regards to *income* Jensen (2006) emphasised that the level of income is a significant determinant of the purchasing power of consumers' food and services, which affect how food is purchased. Can, Günlü and Can (2015) established in their study that income is a significant determinant of fish consumption. Barberger-Gateau *et al.* (2005) showed a significantly increase odds of fish consumption with increase in income level among regular fish consumers. These findings are consistent with the results of our study. Trondsen *et al.* (2004) and Anyanwu (2014) stated that a significant increase in household size shows a positive increase in the consumption of fish, which may be associated with income. However, Adeniyi, Omitoyin and Ojo (2012) Nigerian cross-sectional study found that the higher the participants' level of income the less they spent on fish products, thereby reducing their level of fish intake. This could be due to a preference for other expensive sources of animal protein in some populations.

Social network and support

Marriage

Our Anhui cohort study showed reduced odds of fish consumption among the ‘Never married/Divorced’ participants. In a Taiwan cross-sectional study of participants aged 14-71 years, Li *et al.* (2001) found lower odds of fish consumption among the unmarried participants. Barberger-Gateau *et al*. (2005) also showed reduced odds of fish consumption among the divorced, widow or single participants. Tanskanen *et al.* (2001) observed a reduced intake of fish among the unmarried participants in their cross-sectional study of 3204 Finnish adults aged 25-64 years old. Thong and Solgaard (2017) cross-sectional study of 966 French adults mean aged 42 years (age range 18-65) revealed that their single participants consumed seafood less frequently when compared to those living with family or partner. However, Can, Günlü and Can (2015) cross-sectional study revealed a significantly greater yearly fish intake (1.52 kg) in single compared to married participants. The differences among our Chinese study, and the four reported above (Li *et al.*, 2001; Tanskanen *et al.*, 2001; Barberger-Gateau *et al.*, 2005; Thong and Solgaard, 2017) in comparison with the Turkish study (Can, Günlü and Can, 2015) could be because those who were never married/divorced had a lower household income, and they may have fewer children at home which influences the demand for fish consumption.

Cardiovascular disease and risk factors

Our cohort study showed that older people who smoked would have a lower level of fish consumption. A Finnish cross-sectional study of 3204 adults aged 25-64 years old showed that participants who rarely consumed fish are more likely to smoke (Tanskanen *et al.,* 2001). In a Norwegian cross-sectional study of 3144 participants, a non-significant association was found between smoking habit and intake of very-long-chain omega-3 fatty acids (Johansson *et al.,* 1998). However, Trondsen *et al.* (2004) found a significantly increased consumption of fish with smoking in a cross-sectional study in Norway. These conflicting findings may be influenced by associations between smoking and low socioeconomic status, as well as intentions to maintain healthy lifestyles.

Previous cross-sectional studies reported that fish consumers of more than once a week are significantly less likely to be obese (BMI $\geq$30kg/m^2) (Barberger-Gateau *et al.,* 2005), while another found that participants that rarely consume fish are less likely to be obese (Tanskanen *et al.,* 2001). However, our cohort study showed that older people who were overweight/obese (BMI $\geq$26kg/m^2) at baseline may have increased consumption of fish. This may be due to high income in those with obesity in China.

Barberger-Gateau *et al.* (2005) France cross-sectional study observed that older people who suffered from hypertension consume fish more frequently, but our study showed that those with undetected hypertension at baseline would have a reduced consumption of fish, probably because these people were unaware of their state of health.

Our study shows an increase in fish consumption level among participants with heart disease. It was consistent with the finding from a previous study of 1777 participants aged 25-75 years (Devadawson, Jayasinghe and Sivakanesan, 2015). Devadawson and colleagues (2015) acknowledged that 37% of the participants in the study consumed fish based on curing their heart disease. Previous studies showed that based on health recommendations women with heart disease would have increased consumption of fish (Verbeke and Vackier, 2005). Erdogan, Mol and

Cosansu (2011) also stated that 84.47% of the 972 participants consumed seafood based on its importance to health. This is in line with Can, Günlü and Can (2015) result, where 62.5% of their participants consumed fish based on health reasons. Trondsen *et al.* (2004) confirmed that seafood consumption was influenced by its beneficial impact on health.

Mental Health

Our result shows that older people with depression had a significant decrease in fish consumption level. This is consistent with Barberger-Gateau *et al.* (2005) France cross-sectional study that reported a significant decrease in fish consumption level among their older participants with depressive symptoms. Tanskanen *et al.* (2001) observed in a large population-based study of Finnish adults that the tendency of developing depressive symptoms is significantly higher among infrequent fish consumers. A five-year cohort study of 10,602 men from Northern Ireland and France aged 50-59 years found that higher depressive mood was associated with lower fish intake (Appleton *et al.,* 2007). Astorg *et al.* (2008) cohort study of 13,017 French participants aged 35-60 years observed a significantly reduced risk of any depressive episode among higher consumers of fatty fish or intake of long-chain omega-3 polyunsaturated fatty acid (PUFA).

Previous studies showed a significant reduction in fish consumption among the older participants with lower cognitive performance (Barberger-Gateau *et al.,* 2005). Few studies investigated whether people with dementia had a reduced consumption of fish. As far as we know, our cohort study is the first reporting that older people with dementia had a significantly reduced consumption of fish. The reductions in fish intake among older people with depression or dementia could be due to reduced ability of the participants to choose to cook fish or to purchase fish at a restaurant.

Strengths and Limitations of the study

The main strength of our study lies in its cohort design of identifying possible influencing factors for fish consumption in older population. Our study cohort consists of two random samples of urban and rural Chinese who experienced epidemiological transition with specific characteristics, and we collected data on as many risk factors as possible, including mental health status. These have helped us to identify the determinants of low consumption of fish in older people for increasing the consumption. Our study has limitations. Firstly, there may be a recall bias from participants regarding fish consumption level that occurred during the interview. This would attenuate the associations that we found towards no hypothesis. Secondly, more detailed information about which type of fish intake (e.g. preserved) was not recorded and thus we could not examine its consumption levels. Thirdly, the inability to adjust for total energy intake in our study due to its absence among the variables assessed might have impacted on the overall result. But the adjustment for body weight (WC) in the model and the strong association (e.g. OR 0.10) ensured that our results are robust.

Implication of the Study Findings

Our study offers an insight into how the nutritional status regarding the consumption of inadequate fish protein among older people can be affected by sociodemographic and health factors. There is evidence that no or inadequate consumption of fish could impact on their cognitive function and increase the risk of cardiovascular disease (He *et al.,* 2004a; Larsson and Orsini, 2011) and dementia (Bakre *et al.,* 2018). This result can help the government in their public health policies decision making. This could assist in channeling their resources towards availability and affordability of fish among socio-economically-deprived older populations. Boosting the economy income level through job creation and increasing social welfare might also enhance their overall food intake level including fish consumption, since food cannot be eaten in isolation, thus having a positive impact on their health and well-being. Facilitating the preparation technique of fish could also ease the stress displayed during cooking through provision of ready-made boneless fish products that is accessible to purchase in the market. It is particularly important for the high-risk groups of older people with inadequate consumption of fish, including those with depression and dementia, and this could improve their health and outcomes.

5.6 Conclusion

In conclusion, the findings from our community-based cohort study suggested that reduced consumption of fish in older people was significantly associated with increased age, female gender, smoking, living in rural areas, low levels of education, occupation and income, financial difficulties, low level of life satisfaction, being never married/divorced, and having undetected hypertension, depression and dementia. Targeting these high-risk groups of older people who had low educational level, low-income level and living in a rural area for preventing low consumption of fish would increase their level of consumption.

Table 5.1: Characteristics of participants with different fish consumption levels

Variables	Never eat n (%)	Once a week n (%)	More than twice a week n (%)	≥Once a day n (%)	P value
Demographic factors					
Age (years)					
60-64	96 (24.6)	147 (19.9)	42 (9.2)	8 (7.1)	<0.001
65-69	81 (20.8)	206 (28.0)	169 (37.0)	45 (39.8)	
70-74	83 (21.3)	177 (24.0)	141 (30.9)	40 (35.4)	
75-79	68 (17.4)	135 (18.3)	73 (16.0)	16 (14.2)	
≥80	62 (15.9)	72 (9.8)	32 (7.0)	4 (3.5)	
Sex					
Men	176 (45.1)	320 (43.4)	231 (50.5)	57 (50.4)	0.08
Women	214 (54.9)	417 (56.6)	226 (49.5)	56 (49.6)	
BMI (kg/m^2)					
<20	43 (11.0)	87 (11.8)	40 (8.8)	16 (14.2)	0.150
20-<23	150 (38.5)	225 (30.5)	149 (32.6)	36 (31.9)	
23-<26	117 (30.0)	265 (36.0)	154 (33.7)	37 (32.7)	
≥ 26	80 (20.5)	160 (21.7)	114 (24.9)	24 (21.2)	
Waist Circumference (cm) §					
No Action	267 (68.5)	456 (61.9)	232 (50.8)	54 (47.8)	<0.001
Action Level 1	68 (17.4)	141 (19.1)	113 (24.7)	19 (16.8)	
Action Level 2	55 (14.1)	140 (19.0)	112 (24.5)	40 (35.4)	

Smoking over the last 2 years					
No	251 (64.4)	511 (69.3)	339 (74.2)	84 (74.3)	0.01
Yes	139 (35.6)	226 (30.7)	118 (25.8)	29 (25.7)	
Drinking alcohol over the last 2 years					
No	317 (81.3)	600 (81.4)	355 (77.7)	93 (82.3)	0.380
Yes	73 (18.7)	137 (18.6)	102 (22.3)	20 (17.7)	
Socioeconomic factor					
Urban/rurality					
Urban	28 (7.2)	209 (28.4)	287 (62.8)	98 (86.7)	<0.001
Rural	362 (92.8)	528 (71.6)	170 (37.2)	15 (13.3)	
Educational level					
≥High 2nd School	11 (2.8)	101 (13.7)	148 (32.4)	51 (45.1)	<0.001
Secondary School	12 (3.1)	68 (9.2)	87 (19.0)	26 (23.0)	
Primary School	31 (7.9)	80 (10.9)	56 (12.3)	17 (15.0)	
Illiterate	336 (86.2)	488 (66.2)	166 (36.3)	19 (16.8)	
Main occupation					
No formal job (including business/other/housewife)	9 (2.3)	33 (4.5)	39 (8.5)	12 (10.6)	<0.001
Official/teacher	16 (4.1)	135 (18.3)	202 (44.2)	67 (59.3)	
Manual labourer	10 (2.6)	63 (8.5)	59 (12.9)	19 (16.8)	
Peasant	355 (91.0)	506 (68.7)	157 (34.4)	15 (13.3)	

Income satisfactory					
Very satisfactory	8 (2.1)	32 (4.3)	45 (9.8)	14 (12.4)	<0.001
Satisfactory	19 (4.9)	140 (19.0)	209 (45.7)	65 (57.5)	
Average	16 (4.1)	41 (5.6)	28 (6.1)	17 (15.0)	
Poor	347 (89.0)	524 (71.1)	175 (38.3)	17 (15.0)	
Financial difficulties over the last years					
No	61 (15.6)	237 (32.2)	291 (63.7)	98 (86.7)	<0.001
Yes	329 (84.4)	500 (67.8)	166 (36.3)	15 (13.3)	
Satisfied with life/ current living					
Very satisfactory	179 (45.9)	329 (44.6)	143 (31.3)	22 (19.5)	<0.001
Satisfactory	162 (41.5)	341 (46.3)	276 (60.4)	78 (69.0)	
Average	47 (12.1)	63 (8.5)	35 (7.7)	11 (9.7)	
Poor	2 (0.5)	4 (0.5)	3 (0.7)	2 (1.8)	
Social network and psychosocial factors					
Marriage					
Married	270 (69.2)	554 (75.2)	364 (79.6)	94 (83.2)	0.010
Never married/ Divorced	26 (6.7)	33 (4.5)	9 (2.0)	2 (1.8)	
Widow	94 (24.1)	150 (20.4)	84 (18.4)	17 (15.0)	
Frequency of visiting children or other relatives [&]					
Everyday	28071.8)	490 (66.5)	263 (57.5)	43 (38.1)	<0.001
At least weekly	71 (18.2)	143 (19.4)	131 (28.7)	42 (37.2)	
At least Monthly or less often	27 (6.9)	81 (11.0)	52 (11.4)	24 (21.2)	

<Yearly or Never	12 (3.1)	23 (3.1)	11 (2.4)	4 (3.5)	
Help available when needed					
No	39 (10.0)	66 (9.0)	18 (3.9)	7 (6.2)	0.003
Yes	351 (90.0)	671 (91.0)	439 (96.1)	106 (93.8)	
Cardiovascular disease and risk factors					
Hypertension status					
No hypertension (<140/90 mmHg)	162 (41.5)	313 (42.5)	188 (41.1)	55 (48.7)	<0.001
Undetected	172 (44.1)	269 (36.5)	130 (28.4	23 (20.4	
Untreated	16 (4.1)	39 (5.3)	25 (5.5)	5 (4.4)	
Uncontrolled	34 (8.7)	95 (12.9)	91 (19.9)	19 (16.8)	
Controlled	6 (1.5)	21 (2.8)	23 (5.0)	11 (9.7)	
Hypercholesterolemia					
No	381 (97.7)	710 (96.3)	411 (89.9)	99 (87.6)	<0.001
Yes	9 (2.3)	26 (3.5)	40 (8.8)	13 (11.5)	
Unknown	0	1 (0.1)	6 (1.3)	1 (0.9)	
Diabetes					
No	383 (98.2)	719 (97.6)	434 (95.0)	102 (90.3)	<0.001
Yes	7 (1.8)	16 (2.2)	23 (5.0)	10 (8.8)	
Unknown	0	2 (0.3)	0	1 (0.9)	
Heart diseases (ischaemic, valve disease or others)					
No	369 (94.6)	666 (90.4)	369 (80.7)	95 (84.1)	<0.001
Yes	21 (5.4)	69 (9.4)	86 (18.8)	18 (15.9)	

Unknown	0	2 (0.3)	2 (0.4)	0	
Activity of daily living (score)					
0	377 (96.7)	705 (95.7)	430 (94.1)	109 (96.5)	0.670
1-5	8 (2.1)	21 (2.8	19 (4.2	3 (2.7)	
≥5	5 (1.3)	11 (1.5)	8 (1.8)	1 (0.9)	
Depression and dementia status					
No	271 (69.5)	560 (76.0)	363 (79.4)	93 (82.3)	0.006
Depression subcase	14 (3.6)	30 (4.1)	8 (1.8)	5 (4.4)	
Depression case	25 (6.4)	28 (3.8)	17 (3.7)	1 (0.9)	
Dementia subcase	45 (11.5)	68 (9.2)	50 (10.9)	7 (6.2)	
Dementia case	35 (9.0)	51 (6.9)	19 (4.2)	7 (6.2)	

[&] Data for "Contacting friends in the community" and "Contacting neighbours" showed similar frequencies distributions to those in "Frequency of visiting children or other relatives".

†P-value in the chi square were calculated using the available data i.e. unknowns were excluded; the number (%) of missing data for hypercholesterolemia were 8 (2.3%), diabetes 3 (1.2%), and heart disease 4 (0.7%).

[§] Waist Circumference (WC) (action levels 1 and 2) are classified as 94 and 102cm for men, 80 and 88cm for women (WHO, 2008; Huxley *et al.*, 2010).

Table 5.2: Age-sex adjusted OR of participants who had consumed fish at any level over the past two years

Variables	**Any levels of fish consumption N=1307 (%)**	**Never eat N=390 (%)**	**P value**	**Age-sex adjusted OR**	**95% CI**	**P-value**
Demographic factors						
Age (years)						
60-64	197 (15.1)	96 (24.6)	<0.001	0.40	0.28-0.56	<0.001
65-69	420 (32.1)	81 (20.8)		Ref=1		
70-74	358 (27.4)	83 (21.3)		0.83	0.59-1.16	0.280
75-79	224 (17.1)	68 (17.4)		0.63	0.44-0.91	0.010
≥80	108 (8.3)	62 (15.9)		0.34	0.23-0.50	<0.001
Sex						
Men	608 (46.5)	176 (45.1)		Ref=1		
Women	699(53.5)	214(54.9)	0.63	0.95	0.75-1.19	0.640
BMI (kg/m^2)						
<20	143 (10.9)	43 (11.0)	0.06	1.22	0.82-1.82	0.320
20-<23	410 (31.4)	150 (38.5)		Ref=1		
23-<26	456 (34.9)	117 (30.0)		1.37	1.03-1.81	0.030
≥ 26	298 (22.8)	80 (20.5)		1.31	0.96-1.80	0.090

Waist Circumference (cm)						
No Action	742 (56.8)	267 (68.5)	<0.001	Ref=1		
Action Level 1	273 (20.9)	68 (17.4)		1.47	1.07-2.03	0.020
Action Level 2	292 (22.3)	55 (14.1)		1.95	1.38-2.75	<0.001
Smoking over the last 2 years						
No	934 (71.5)	251 (64.4)	0.007	Ref=1		
Yes	373 (28.5)	139 (35.6)		0.62	0.46-0.83	0.001
Drinking alcohol over the 2 years						
No	1048 (80.2)	317 (81.3)	0.63	Ref=1		
Yes	259 (19.8)	73 (18.7)		1.03	0.75-1.41	0.860
Socioeconomic factor						
Urban/rurality						
Urban	594 (45.4)	28 (7.2)	<0.001	Ref=1		
Rural	713 (54.6)	362 (92.8)		0.10	0.07-0.15	<0.001
Educational level						
≥High 2nd School	300 (23.0)	11 (2.8)	<0.001	Ref=1		
Secondary School	181 (13.8)	12 (3.1)		0.56	0.24-1.29	0.170
Illiterate/ Primary School	826 (63.2)	367 (94.1)		0.09	0.05-0.17	<0.001
Main occupation						
No formal job (including business/other/housewife)	84 (6.4)	9 (2.3)	<0.001	0.37	0.16-0.86	0.020

Official/teacher	404 (30.9)	16 (4.1)		Ref=1		
Manual labourer	141 (10.8)	10 (2.6)		0.55	0.24-1.25	0.150
Peasant	678 (51.9)	355 (91.0)		0.08	0.05-0.14	<0.001
Income satisfactory						
Very satisfactory	91 (7.0)	8 (2.1)	<0.001	0.53	0.22-1.25	0.150
Satisfactory	414 (31.7)	19 (4.9)		Ref=1		
Average	86 (6.6)	16 (4.1)		0.25	0.12-0.51	<0.001
Poor	716 (54.8)	347 (89.0)		0.10	0.06-0.17	<0.001
Financial difficulties over the last years						
No	626 (47.9)	61 (15.6)	<0.001	Ref=1		
Yes	681 (52.1)	329 (84.4)		0.23	0.17-0.31	<0.001
Satisfied with life/ current living						
Very satisfactory	494 (37.8)	179 (45.9)	0.001	0.71	0.55-0.91	0.006
Satisfactory	695 (53.2)	162 (41.5)		Ref=1		
Average/ Poor	118 (9.0)	49 (12.6)		0.55	0.38-0.81	0.002
Social network and psychosocial factors						
Marriage						
Married	1012 (77.4)	270 (69.2)	0.001	Ref=1		
Never married/ Divorced	44 (3.4)	26 (6.7)		0.46	0.27-0.78	0.004

Widow	251 (19.2)	94 (24.1)		0.78	0.58-1.03	0.080
Frequency of visiting children or other relatives						
Everyday	796 (60.9)	280 (71.8)	0.001	0.71	0.53-0.96	0.030
At least weekly	316 (24.2)	71 (18.2)		Ref=1		
At least Monthly or less often	157 (12.0)	27 (6.9)		1.37	0.84-2.22	0.210
<Yearly or Never	38 (2.9)	12 (3.1)		0.75	0.37-1.53	0.430
Contacting friends in the community						
<Yearly or Never	62 (4.7)	23 (5.9)	0.58	0.72	0.43-1.22	0.220
At least Monthly or less often	310 (23.7)	97 (24.9)		0.88	0.66-1.19	0.410
At least weekly	527 (40.3)	144 (36.9)		Ref=1		
Everyday	408 (31.2)	126 (32.3)		0.85	0.65-1.12	0.250
Contacting neighbours						
<Yearly or Never	32 (2.4)	4 (1.0)	0.10	2.00	0.69-5.81	0.20
At least Monthly or less often	382 (29.2)	100 (25.6)		1.13	0.85-1.52	0.40
At least weekly	469 (35.9)	141 (36.2)		Ref=1		
Everyday	424 (32.4)	145 (37.2)		0.87	0.66-1.14	0.310
Help available when needed						
No	91 (7.0)	39 (10.0)	0.05	Ref=1		
Yes	1216 (93.0)	351 (90.0)		1.42	0.95-2.13	0.090

Cardiovascular disease and risk factors						
Hypertension status						
No hypertension (<140/90 mmHg)	556 (42.5)	162 (41.5)	<0.001	Ref=1		
Undetected	422 (32.3)	172 (44.1)		0.73	0.56-0.94	0.010
Untreated	69 (5.3)	16 (4.1)		1.18	0.66-2.11	0.570
Uncontrolled	205 (15.7)	34 (8.7)		1.59	1.06-2.39	0.030
Controlled	55 (4.2)	6 (1.5)		2.28	0.96-5.43	0.060
Hypercholesterolemia						
No	1220 (93.3)	381 (97.7)	0.004	Ref=1		
Yes	79 (6.0)	9 (2.3)		2.20	1.09-4.46	0.030
Unknown	8 (0.6)	0				
Diabetes						
No	1255 (96.0)	383 (98.2)	0.104	Ref=1		
Yes	49 (3.7)	7 (1.8)		1.80	0.80-4.03	0.160
Unknown	3 (0.2)	0				
Heart diseases (ischaemic, valve disease or others)						
No	1130 (86.5)	369 (94.6)	<0.001	Ref=1		
Yes	173 (13.2)	21 (5.4)		2.48	1.55-3.98	<0.001
Unknown	4 (0.3)	0				

Activity of daily living (score)						
0	1244 (95.2)	377 (96.7)	0.42	Ref=1		
1-5	43 (3.3)	8 (2.1)		1.50	0.69-3.24	0.310
≥5	20 (1.5)	5 (1.3)		1.26	0.46-3.46	0.650
Depression and dementia status						
No	1016 (77.7)	271 (69.5)	.006	Ref=1		
Depression subcase	43 (3.3)	14 (3.6)		0.86	0.46-1.62	0.650
Depression case	46 (3.5)	25 (6.4)		0.49	0.29-0.83	0.010
Dementia subcase	125 (9.6)	45 (11.5)		0.78	0.53-1.13	0.190
Dementia case	77 (5.9)	35 (9.0)		0.65	0.43-1.01	0.050

Table 5.3: Multivariate adjusted OR* of participants who had consumed fish at any level over the past two years

Variables	Adjusted OR*	95% CI	P value
Demographic Factors			
Age (years)			
60-64	0.44	0.31- 0.62	<0.001
65-69	Ref=1		
70-74	0.84	0.60-1.18	0.320
75-79	0.64	0.45-0.92	0.020
≥80	0.35	0.24-0.52	<0.001
Sex			
Men	Ref=1		
Women	0.63	0.47-0.84	0.002
Waist Circumference (cm)			
No Action	Ref=1		
Action Level 1	1.40	1.01-1.93	0.040
Action Level 2	1.89	1.34-2.68	<0.001

Smoking over the last 2 years			
No	Ref=1		
Yes	0.65	0.48-0.88	0.005
Socioeconomic factor			
Urban/rurality			
Urban	Ref=1		
Rural	0.10	0.07-0.15	<0.001
Educational level			
≥High 2nd School	Ref=1		
Secondary School	0.57	0.25-1.32	0.190
Illiterate/ Primary School	0.10	0.05-0.19	<0.001
Main occupation			
No formal job (including business/other/housewife)	0.38	0.16-0.89	0.030
Official/teacher	Ref=1		
Manual labourer	0.57	0.25-1.29	0.180
Peasant	0.08	0.05-0.14	<0.001

Income satisfactory			
Very satisfactory	0.53	0.23-1.26	0.150
Satisfactory	Ref=1		
Average	0.26	0.13-0.53	<0.001
Poor	0.11	0.07-0.18	<0.001
Financial difficulties over the last years			
No	Ref=1		
Yes	0.25	0.18-0.34	<0.001
Satisfied with life/ current living			
Very satisfactory	0.73	0.57-0.94	0.010
Satisfactory	Ref=1		
Average/ Poor	0.56	0.38-0.82	0.003
Marriage			
Married	Ref=1		
Never married/ Divorced	0.48	0.28-0.81	0.006
Widow	0.79	0.59-1.05	0.100

Frequency of visiting children or other relatives[&]			
Everyday	0.77	0.57-1.04	0.080
At least weekly	Ref=1		
At least Monthly or less often	1.39	0.85-2.27	0.190
<Yearly or Never	0.78	0.38-1.60	0.510
Help available when needed			
No	Ref=1		
Yes	1.44	0.96-2.15	0.080
Cardiovascular disease and risk factors			
Hypertension status			
No hypertension (<140/90 mmHg)	Ref=1		
Undetected	0.71	0.55-0.91	0.008
Untreated	1.10	0.61-1.98	0.750
Uncontrolled	1.34	0.88-2.04	0.170
Controlled	1.89	0.79-4.54	0.160

Hypercholesterolemia			
No	Ref=1		
Yes	1.87	0.92-3.82	0.090
Unknown			
Heart diseases (ischaemic, valve disease or others)			
No	Ref=1		
Yes	2.33	1.44-3.75	0.001
Unknown			
Depression and dementia status			
No	Ref=1		
Depression subcase	0.83	0.44-1.57	0.570
Depression case	0.50	0.29-0.84	0.009
Dementia subcase	0.73	0.50-1.07	0.100
Dementia case	0.64	0.41-0.98	0.040

***** adjusted for age, sex, waist circumference and smoking at the baseline

[&] Data for "Contacting friends in the community" and "Contacting neighbours" showed no significant ORs.

Table 5.4: Multivariate adjusted OR* of participants who had different levels of fish consumption over the past two years

Variables	Once a week			More than twice a week			>= Once a day		
	Adjusted OR*	**95% CI**	**P value**	**Adjuste d OR***	**95% CI**	**P value**	**Adjuste d OR***	**95% CI**	**P value**
Demographic Factors									
Age (years)									
60-64	0.63	0.44-0.91	0.010	0.23	0.15-0.37	<0.001	0.16	0.07-0.37	<0.001
65-69	Ref=1			Ref=1			Ref=1		
70-74	0.86	0.59-1.24	0.410	0.80	0.54-1.18	0.260	0.87	0.50-1.52	0.630
75-79	0.78	0.53-1.15	0.210	0.53	0.34-0.82	0.004	0.42	0.21-0.84	0.010
≥80	0.46	0.30-0.71	<0.001	0.26	0.15-0.44	<0.001	0.12	0.04-0.35	<0.001
Sex									
Men	Ref=1			Ref=1			Ref=1		
Women	0.85	0.62-1.17	0.330	0.39	0.27-0.57	<0.001	0.34	0.19-0.61	<0.001
Waist Circumference (cm)									
No Action	Ref=1			Ref=1			Ref=1		
Action Level 1	1.14	0.81-1.63	0.460	2.08	1.39-3.09	<0.001	1.34	0.69-2.61	0.380
Action Level 2	1.42	0.98-2.07	0.070	2.93	1.91-4.49	<0.001	4.70	2.53-8.75	<0.001

Smoking over the last 2 years									
No	Ref=1			Ref=1			Ref=1		
Yes	0.79	0.57-1.08	0.140	0.51	0.35-0.74	<0.001	0.43	0.24-0.77	0.004
Socioeconomic factor									
Urban/rurality									
Urban	Ref=1			Ref=1			Ref=1		
Rural	0.20	0.13-0.31	<0.001	0.05	0.03-0.08	<0.001	0.01	0.00-0.02	<0.001
Educational level									
≥High 2nd School	Ref=1			Ref=1			Ref=1		
Secondary School	0.65	0.27-1.58	0.350	0.55	0.23-1.30	0.170	0.62	0.23-1.66	0.340
Illiterate/Primary School	0.19	0.10-0.36	<0.001	0.06	0.03-0.12	<0.001	0.03	0.01-0.07	<0.001
Main occupation									
No formal job (including business/other/housewife)	0.43	0.17-1.06	0.070	0.36	0.15-0.89	0.030	0.38	0.13-1.12	0.080
Official/teacher	Ref=1			Ref=1			Ref=1		
Manual labourer	0.72	0.31-1.70	0.460	0.54	0.23-1.28	0.160	0.54	0.19-1.51	0.240

Peasant	0.17	0.10-0.30	<0.001	0.04	0.03-0.08	<0.001	0.01	0.003-0.02	<0.001
Income satisfactory									
Very satisfactory	0.57	0.23-1.43	0.230	0.51	0.21-1.25	0.140	0.58	0.20-1.66	0.310
Satisfactory	Ref=1			Ref=1			Ref=1		
Average	0.35	0.17-0.75	0.010	0.18	0.08-0.39	<0.001	0.32	0.13-0.80	0.010
Poor	0.23	0.14-0.38	<0.001	0.06	0.04-0.10	<0.001	0.02	0.01-0.04	<0.001
Financial difficulties over the last years									
No	Ref=1			Ref=1			Ref=1		
Yes	0.44	0.31-0.62	<0.001	0.14	0.10-0.21	<0.001	0.04	0.02-0.07	<0.001
Satisfied with life/ current living									
Very satisfactory	0.91	0.70-1.19	0.490	0.52	0.38-0.72	<0.001	0.28	0.16-0.49	<0.001
Satisfactory	Ref=1			Ref=1			Ref=1		
Average/Poor	0.62	0.41-0.95	0.030	0.49	0.29-0.80	0.005	0.60	0.29-1.24	0.170
Social network and psychosocial factors									
Marriage									
Married	Ref=1			Ref=1			Ref=1		

Never married/Divorced	0.64	0.37-1.10	0.110	0.24	0.10-0.54	0.001	0.21	0.05-0.97	0.046
Widow	0.80	0.59-1.09	0.160	0.82	0.57-1.18	0.290	0.76	0.41-1.41	0.380
Frequency of visiting children or other relatives[&]									
Everyday	0.93	0.67-1.29	0.670	0.65	0.45-0.94	0.020	0.32	0.19-0.56	<0.001
At least weekly	Ref=1			Ref=1			Ref=1		
At least Monthly or less often	1.58	0.93-2.67	0.090	1.02	0.57-1.83	0.950	1.50	0.70-3.19	0.300
<Yearly or Never	0.98	0.46-2.09	0.950	0.59	0.23-1.48	0.260	0.79	0.22-2.87	0.720
Help available when needed									
No	Ref=1			Ref=1			Ref=1		
Yes	1.14	0.74-1.73	0.560	3.00	1.63-5.52	<0.001	1.91	0.79-4.61	0.150
Cardiovascular disease and risk factors									
Hypertension status									
No hypertension (<140/90 mmHg)	Ref=1			Ref=1			Ref=1		

Undetected	0.80	0.61-1.05	0.110	0.60	0.43-0.84	0.003	0.34	0.19-0.61	<0.001
Untreated	1.17	0.63-2.18	0.620	0.96	0.47-1.99	0.920	0.79	0.25-2.49	0.680
Uncontrolled	1.21	0.77-1.90	0.400	1.54	0.95-2.51	0.080	1.03	0.49-2.15	0.940
Controlled	1.47	0.57-3.77	0.430	2.33	0.87-6.22	0.090	3.51	1.04-11.89	0.040
Hypercholesterolemia									
No	Ref=1			Ref=1			Ref=1		
Yes	1.21	0.55-2.65	0.640	2.19	1.02-4.70	0.040	3.82	1.45-10.02	0.007
Unknown									
Heart diseases (ischaemic, valve disease or others)									
No	Ref=1			Ref=1			Ref=1		
Yes	1.75	1.05-2.93	0.030	3.22	1.89-5.49	<0.001	2.95	1.39-6.27	0.005
Unknown									
Depression and dementia status									
No	Ref=1			Ref=1			Ref=1		
Depression subcase	1.02	0.53-1.97	0.950	0.39	0.15-1.05	0.060	0.93	0.28-3.08	0.900
Depression case	0.51	0.29-0.90	0.020	0.50	0.25-1.01	0.050	0.07	0.01-0.54	0.010

Dementia subcase	0.72	0.48-1.08	0.110	0.80	0.50-1.27	0.340	0.48	0.19-1.19	0.110
Dementia case	0.71	0.45-1.12	0.140	0.42	0.23-0.78	0.006	0.71	0.29-1.75	0.450

* adjusted for age, sex, waist circumference and smoking at baseline

[&] Data for "Contacting friends in the community" and "Contacting neighbours" showed no significant ORs.

CHAPTER SIX: ASSOCIATION OF FISH CONSUMPTION IN OLDER AGE WITH DEMENTIA: MULTI-PROVINCE STUDY IN CHINA AND A META-ANALYSIS FOR THE WORLD LITERATURE

6.1 Introduction

Previous studies showed that eating fish was related to reduced risks of cardiovascular diseases (CVD) (e.g. coronary heart disease (CHD) (He *et al.*, 2004), stroke (Larsson and Orsini, 2011), respiratory disease (Yang, Xun and He, 2013) and depression (Li, Liu and Zhang, 2016). There are also some studies suggesting that fish consumption could improve cognitive function across the life course (Prince *et al.*, 2014), mainly in young people (Eilander *et al.*, 2007).

Since fish fatty acids are important constituents for proper brain functioning and neurocognitive development (Salem *et al.*, 2001), there has been an increase in research investigating whether fish consumption could reduce the risk of dementia (Lopez *et al.*, 2011). However, the findings from those studies are not consistent (Morris *et al.*, 2005; van Gelder *et al.*, 2007). Some studies suggested that fish consumption was associated with a reduced risk of dementia (Barberger-Gateau *et al.*, 2002; Morris *et al.*, 2003), while others did not show such an association (Engelhart *et al.*, 2002; van de Rest *et al.*, 2009). Previous studies on the association of fish consumption and dementia are predominantly from high income countries, where the characteristics of population would make difficulties in dealing with confounding effects including high levels of cardiovascular diseases and risk factors on the association between fish consumption and dementia risk, and the findings could not be generalised to other countries. There is lack of data (Zhang *et al.*, 2016) from low- and middle-income countries (LMIC), where people have high risk of dementia but low level of fish consumption (Prince *et al.*, 2015). Thus, in this Chapter I examined the data from China to contribute to the knowledge in this field.

Also, I carried out a meta-analysis including the data from China to investigate the association of fish consumption with risk of dementia. Although there were meta-analyses published previously (Cao *et al.*, 2015; Wu *et al.*, 2015; Zhang *et al.*, 2016) to investigate the association, the inferences from those meta-analysis studies were hindered by several potential limitations, for instance, missing relevant key publications (Lopez *et al.*, 2011). In the present work, I performed a new meta-analysis to investigate the association of fish consumption with risk of dementia and its dose-response relationship, and to examine any differences in the association between high income countries and LMIC.

6.2 Methods

6.2.1 Multi-province health survey study of older people in China

I analysed data from the multi-province health survey study of dementia in China. The methods of the study, populations and interview outcomes have been fully reported before (Chen, 2012; Chen *et al.*, 2013) and in Chapter 3 the methodology section above (3.6.1.6). In brief, during 2007-2010, we carried out a large-scale health survey study of older people in the provinces of Guangdong, Heilongjiang, Shanghai and Shanxi, Anhui and Hubei in China to investigate prevalence, risk factors and care of dementia and other chronic conditions (Chen *et al.*, 2012; Chen *et al.*, 2013).

6.2.1.1 The Four-Province Study

In 2008-2009 we selected one rural and one urban community from each of the four provinces (Guangdong, Heilongjiang, Shanghai, Shanxi) as the study fields. We tried to recruit no fewer than 500 participants in each community and employed a cluster randomised sampling method to choose residential communities (the district in urban areas and the village in rural) from each of the four provinces. The target population consisted of residents aged ≥60 years living in the area for at least 5 years. Based on the residency list of the committees of the villages and the districts, we recruited a total of 4314 participants with an overall response rate of 93.8%. The local survey team interviewed the participants at home. The main interview included a general health and risk factors record, the Geriatric Mental State (GMS) questionnaire (Copeland *et al.*, 2002) and other components of the 10/66 algorithm dementia research package (Prince *et al.*, 2003). We carried out a two-phase interview to save our research resources. In phase one, we completed the general health and risk factors record, the GMS, the Community Screening Instrument for Dementia (CSI-D) cognitive test and Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Using three of the four constituent components of the 10/66 algorithm (i.e. data of GMS-AGECAT, the CSI-D cognitive test and CERAD interview), we calculated a probability of possible dementia for each participant. In phase two, we selected the top 15% of the population who had the highest probability of having 'dementia' as 'probable cases' and a random sample of 5% of the rest as 'probable non-cases' for subsequent interviews in each province. The interview team completed the CSI-D informant interview for the selected participants.

6.2.1.2 The Anhui study

Using the same interview approach as that in the four-province study, we completed interviews of 1757 older people from the third wave survey of the Anhui cohort (Chen *et al.,* 2013), the initial number of which was 3336 participants at baseline aged ≥60 years who were randomly recruited in 2001 and 2003, respectively.

6.2.1.3 The Hubei study

In 2010-2011 we extended the project to include the Hubei province (Chen *et al.*, 2013). We used the same protocol and interview materials as in the four-province study but interviewed all participants in a one stage phase using the full 10/66 methods. We recruited 1,001 participants aged ≥ 60 years and achieved a response rate of 91.8%.

6.2.1.4 Risk factors

In the general health and risk factors questionnaire interview, we recorded details relating to socio-demographic characteristics, lifestyle, social networks and support, histories of chronic diseases and risk factors (Chen *et al.*, 2005). We measured height, weight, waist circumference and blood pressure for all participants. In the interview, we asked each participant for details of dietary intakes, including rice, wheat flour, meat, fish, egg, fresh vegetables, fruits, chilli peppers, garlic, ginger and different types of vegetable oil. All participants were required to provide the answer to the frequency of fish consumption in the past two years: (i) never eat; (ii) ≤once weekly; (iii) >once per weekly and < daily; (iv) once daily; and (v) ≥ twice daily.

6.2.1.5 Diagnosis of dementia

The GMS data were analysed by a computer program-assisted diagnosis, the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT), to assess the principal mental disorders in the study participants (Copeland *et al.*, 2002). We employed the 10/66 dementia algorithm to diagnose dementia, which included the data from the GMS-AGECAT diagnostic output, the CSI-D cognitive test score (COGSCORE), the CSI-D informant interview (RELSCORE), and the CERAD ten-word list learning task with delayed recall (Prince *et al.*, 2003; Prince *et al.*, 2008). We used a cut-off point of probability (≥0.25) derived from the full 10/66 algorithm to diagnose dementia, which has been validated in China (Rodriguez *et al.*, 2008). Three hundred and twenty-six participants were diagnosed to have dementia.

6.3 Data Analysis

We examined the distributions of the baseline socio-demographic and clinical characteristics of participants with different levels of fish consumption documented using chi-squared test for categorical variables and one-way analysis of variance for continuous outcome variables. We employed a binary logistic regression model to calculate Odd Ratios (ORs) and their 95% Confidence Intervals (CIs) of dementia in participants with different levels of fish consumption in comparison to those with no fish consumption over the past 2 years. In the model, we adjusted for age, sex, province, urban/rural areas, education level, smoking status and stroke. The data analysis was conducted using the statistical software package IBM SPSS Statistics version 20.

6.4 Meta-analysis

Data (Odds ratios (ORs), Rate ratios or Hazard ratios (HRs) and their 95% CIs) were pooled from published studies and the new study. All these measures and their 95% CIs were pooled together as a relative risk (RR) with the assumption of achieving a common unit of comparison. We analysed the data grouped by studied population in each of the study which we selected to investigate all types of dementia in relation to fish consumption. The studied population was defined as each individual sample in the study according to its place (country, regions), time (years) and person (e.g. ethnicity) where applicable. A random effect model was employed if the heterogeneity of the within and between studies variation were significant; otherwise, a fixed effect model was used. Publication bias was evaluated using the Egger's regression (Egger *et al.*, 1997). First, we tried to assess an overall RR of dementia in participants who consumed fish in comparison with those who did not. If the article only gave the RRs in different levels of fish consumption, we took the figure from the highest fish consumption group for analysis. If the article only gave the figures from the continuous data analysis of fish consumption or from only high vs low levels of fish consumption, we took them in the meta-analysis. Second, we stratified the identified studies for meta-analysis according to the number of the groups of fish consumption measured at differing levels. This would help to examine differences in the RR among studies with different levels of fish consumption data analysis. Third, we investigated a dose-response association between fish consumption and risk of dementia according to low, middle and high consumption *v.* no/rare consumption. Where an article only gave the figure from the continuous data analysis of fish consumption or from only two groups of fish consumption (high *v.* low level) we took it in the middle level of fish consumption for the meta-analysis. If the article only provided the data of RR and 95% CI from the middle and high levels of fish consumption *v.* no/rare consumption, we took them in the middle and high group levels for pooling the data. We examined any differences in the impact of fish consumption on the risk of dementia among LMIC and high-income countries. We also investigated any influence of the study design (cases-control studies, cross-sectional studies, and cohort studies) and duration of the cohort follow up on the association. We repeated above analyses for AD, where the data were available. All analyses were performed using the statistical software package STATA version 14.2.

6.5 Results

6.5.1 The six provinces study of China

Of 7072 participants, 6981 (98.7%) provided information on fish consumption. Their mean age was 72.2 (SD 7.6) years and 55.6% were women. In total, 1528 participants (21.9%) did not eat fish over the past two years, 2631 (37.7%) consumed fish once weekly, 1938 (27.8%) ≥twice weekly and 884 (12.7%) ≥ once daily. We examined the demographic characteristics of participants in each of these four groups (data not shown). Table 6.1 shows numbers, percentages and OR of dementia in participants with different levels of fish consumption. The risk of dementia decreased with increased consumption of fish, although participants who consumed fish ≥once daily had the highest prevalence of dementia. After adjusting for age, sex, stroke and other confounding factors, we found that participants with different levels of fish consumption had a reduced risk of dementia (the details of OR shown in Table 6.1), but there seemed no significant 'dose-response' relationship. Participants with any level of fish consumption had a 27% significant reduction in the risk of dementia (adjusted OR 0.73, 95% CI 0.64-0.99) in comparison with those who did not consume fish over the past two years.

6.5.2 Meta-analysis

After excluding two studies that did not present the effect sizes (Conquer *et al.,* 2000; Tully *et al.,* 2003) we took data from fifteen studied populations reported within nine published studies, and the data from the six-provinces study of China for the meta-analysis. Figure 6.2 shows a forest plot of the findings of the association between fish consumption and dementia risk. In total, 3139 dementia cases in 40,668 participants were analysed. Data from these studied populations suggested little variability in the associated effects between studies with only one study showing an increased risk (albeit not statistically significant) of dementia associated with higher fish consumption. The fixed effect model analysis showed that there was a 20% reduction in the risk of dementia in participants who consumed fish (or consumed fish at a higher level) compared to those who did not eat fish (or who consumed fish at a lower level). There was little evidence of publication bias; the Egger method of bias estimate showed a p-value of 0.597 (see Figure 6.4).

Data from different study designs or from different measures of fish consumption showed no significant differences in RR for dementia risk in relation to fish consumption (Table 6.2). The association of fish consumption with dementia risk was similar between high income countries (RR 0.83, 0.71-0.97) and LMIC (RR 0.79, 0.72-0.88; Table 6.2).

Of sixteen studied populations from nine articles and the new study in China for the meta-analysis, two (Barberger-Gateau *et al.,* 2007; Albanese *et al.,* 2009) showed a significant trend for a dose-response relationship. The pooled data showed that compared to no consumption of fish, RR of dementia was significantly reduced in participants with a low level of fish consumption (0.84, 0.72-0.98), with a middle level of fish consumption (0.78, 0.68-0.90) and with a high level of fish consumption (0.77, 0.61-0.98), suggesting a dose-response relationship (Table 6.3).

In all seven studied populations which examined the risk of AD specifically in relation to fish consumption (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005; Schaefer et al., 2006; Barberger-Gateau *et al.,* 2007; Devore *et al.,* 2009; Lopez, Kritz-Silverstein and Barrett-Connor, 2011), the pooled data (in total 1105 cases of AD) showed a significant impact of fish consumption on reduced risk of AD (0.73, 0.65-0.82; the forest plot is shown in Figure 6.3). All studies were undertaken in high income countries and were of cohort design. The patterns for the impact of fish consumption on reduced risk of AD (see Table 6.4) were similar to those in all dementia, and it may have a stronger dose-response relationship in comparison with those in dementia (see Table 6.3).

6.6 Discussion

This Chapter study examined the data from a large-scale health survey of dementia in China and completed a meta-analysis to assess the association of fish consumption with dementia and AD risks in countries with different levels of income. We found that increased consumption of fish was significantly associated with a reduced risk of dementia, and there was a stronger dose-response relationship between fish consumption and a reduced risk of AD.

The observed inverse association between the risk of dementia and fish consumption is biologically plausible. Fish is the major dietary source of omega-3 polyunsaturated fatty acids (PUFAs), which comprise docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), being collectively called the 'fish fatty acids' (Uauy and Dangour, 2006; Connor and Connor, 2007). Previous studies have suggested the preventive effect of fish consumption and its constituent omega-3 fatty acid on CVD, through inflammation reduction, blood pressure reduction and endothelial function enhancement (Larsson and Orsini, 2011). Fish consumption has been shown to have a preventive effect on reducing the risks of CHD (RR 0.62, 95% CI 0.46-0.82) (He *et al.*, 2004) and stroke (RR 0.94, 95% CI 0.89-0.99) (Larsson and Orsini, 2011). These are co-morbidities associated with dementia (Newman *et al.*, 2005). Therefore, reducing these diseases may be one of the pathways for the preventive impact of fish consumption on dementia.

6.6.1 Strengths and Limitations of the study

The main strength of this paper is the inclusion of both original data from a large-scale health survey in China and data from all other relevant studies worldwide based on a systematic search and review. Older Chinese citizens have higher levels of socioeconomic deprivation, but low levels of cardiovascular risk factors (e.g. obesity) and depression (Chen *et al.*, 2005). These special population characteristics of older Chinese residents helped to assess the association of fish consumption with the risk of dementia. Our systematic literature review and meta-analysis focused on determining the association between fish consumption and risk of dementia worldwide. The previous meta-analysis papers (Cao *et al.,* 2015; Wu *et al.,* 2015; Zhang *et al.,* 2016) investigated the associations of both fish and omega-3 PUFA with combined mild and severe cognitive impairment (e.g. mild cognitive impairment (MCI), Parkinson disease, all-type dementia and AD), not specifying exposure or outcomes, and failed to include some relevant studies (Lopez, Kritz-Silverstein and Barrett-Connor, 2011). In comparison with those previous reviews and meta-analyses (Cao *et al.,* 2015; Wu *et al.,* 2015; Zhang *et al.,* 2016), our meta-analysis elaborated specifically on the impact that the consumption of fish has on dementia and AD development. The findings were based on the literature search without any limited selection and identified all eligible studies further including a new study from China (LMIC), which compensated for the scarce data from the LMIC generally. Adding in the new community-based cross-sectional study from China made our meta-analysis findings more robust and generalisable.

Our study has several potential limitations. First, the six-province health survey data were cross-sectional, and the causal-relationship between fish consumption and dementia risk could not be assessed. However, the findings of the six-province study were similar to those in the cohort studies (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005; Schaefer *et al.,* 2006; Barberger-Gateau *et al.,* 2007; Devore *et al.,* 2009; Lopez, Kritz-Silverstein and Barrett-Connor, 2011). Second, like the majority of previous studies, in the six-province survey we did not have information on different types (lean, fatty-fish, fried fish and seafood) and quantity of fish consumed, which may hinder our inferences on specific types of fish and dementia. But overall, total fish consumption was significantly and inversely associated with dementia risk. We need further studies on specific types of fish consumption in relation to reduced dementia risk to warrant making more informative recommendations to the public. Third, the identified studies used different levels of fish consumption for data analysis, making it difficult to assess the presence of a dose-response relationship between fish consumption and dementia risk. Using the RR data from the group with the highest-level of fish consumption in some studies may be over-estimating the overall effect of fish consumption on dementia risk. However, when stratifying the articles for meta-analysis according to the number of groups of fish consumption level, we did not find that there was a trend of reduced risk of dementia or AD with increased number of the fish consumption level groups (Table 6.2, and Table 6.4). If we included all RR from different levels of fish consumption to pool the data (see Figure 5), the finding of the overall impact was not substantially changed (OR 0.80, 95% CI 0.75-0.87).

In the current systematic literature review we noted that these eleven identified articles plus the 6-provinces study in China had various study designs, different locations, and various types of FFQ to measure their fish intake. As the studies included in this meta-analysis were observational, the outcome of the current study was examined using the review guidelines of Bradford Hill (Hill, 1965) to provide evidence of a direct and causal relationship between fish consumption and risk of dementia and/or AD.

6.6.2 How strong are the associations?

The majority of the identified studies showed a moderate to high association of fish consumption with reduced risk of dementia (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005; Schaefer *et al.,* 2006; Barberger-Gateau *et al.,* 2007; Albanese *et al.,* 2009; Devore *et al.,* 2009; Kim *et al.,* 2010; Lopez, Kritz-Silverstein and Barrett-Connor, 2011) after adjusting for possible confounders. Only one showed a weak or no association between fish consumption and the risk of dementia (Devore *et al.*, 2009). Our pooled data analysis showed a 20% to 30% increase in the risk of dementia and AD in people who did not eat fish in comparison with those who did. The magnitude of the association between fish consumption and the risk of dementia is similar to the impacts of environmental tobacco smoke (ETS) on the incidence of coronary heart disease (25% increased risk (He *et al.*, 1999), and on lung cancer (27% increased risk (Taylor, Najafi and Dobson, 2007)), and both have been taken as having a causal relationship with environmental tobacco smoke exposure.

6.6.3 How consistent are the reported studies?

Of the seventeen studied populations in this current review, fifteen reported a reduction in the risk of dementia with a moderate to high intake of fish and adjusting for possible confounders (Conquer *et al.,* 2000; Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Tully *et al.,* 2003; Huang *et al.,* 2005; Schaefer *et al.,* 2006; Barberger-Gateau *et al.,* 2007; Lopez, Kritz-Silverstein and Barrett-Connor, 2011). Two of the studies also showed a significant inverse association of fish consumption with the risk of mild to severe dementia and AD development, when the plasma phospholipid and the serum level of the AD participants were assessed for their DHA and EPA levels (Conquer *et al.,* 2000; Tully *et al.,* 2003). A significant reduction was also observed in the six-province study from China. A consistent inverse association between fish consumption and dementia risk was observed in all seven countries that took part in the 10/66 dementia research group study, except India (Albanese *et al.,* 2009). Our meta-analysis for these reviewed studies showed a high level of homogeneity, suggesting their consistent data.

Moreover, there are similar findings of the impact of fish consumption on cognitive function in children. Cohen *et al.* (2005) analysed the data of a randomised control trial (RCT) and demonstrated a 0.13-points increase in the Intelligence Quotient (IQ) of children when mothers received a DHA supplement of 100mg/day. A review by Eilander *et al.* (2007) established enhanced cognitive development in infants and children after maternal supplementation with long-chain omega-3 PUFA during pregnancy and lactation although they had inadequate evidence for an association with children over 2 years old. Ryan *et al*. (2010) also indicated in their review that neurocognitive development during childhood is enhanced when pregnant and lactating mothers are supplemented with DHA. These would support our findings of the impact of fish consumption on reduced risk of dementia.

6.6.4 How specific are the proposed fish consumptions and the response to outcome?

Of these identified articles, a few studies (Barberger-Gateau *et al.,* 2002; Huang *et al.,* 2005; Barberger-Gateau *et al.,* 2007) investigated the fish intake based on fatty, lean, fried fish and seafood. The varying consumption of these types of fish might have affected the outcome of these studies. Huang *et al.* (2005) revealed a 28% reduction in the risk of developing dementia after the intake of fatty fish, while the consumption of lean fried fish produced no significant beneficial effect. The two major fish fatty acid constituents (DHA and EPA) were associated with a reduced risk of developing dementia and cognitive decline (Dangour *et al.*, 2009; Wu *et al.,* 2015). The dose-response impact of fish consumption on specific dementia, i.e. AD, seemed to be stronger.

6.6.5 Is there a temporal relationship between exposure and response?

The observed association between fish consumption and dementia was prominent in all the prospective cohort studies (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005;

Schaefer *et al.,* 2006; Barberger-Gateau *et al.,* 2007; Devore *et al.,* 2009; Lopez, Kritz-Silverstein and Barrett-Connor, 2011), demonstrating a temporal association which signified that an exposure preceded the outcome. In the USA, Huang *et al.* (2005) followed up 2233 participants for 5.4 years and identified 378 new cases of dementia; the RR in participants with fish consumption was 0.79 (95% CI 0.53-1.20). The Rotterdam study followed up 5395 participants for 9.6 years and observed that 465 dementia cases developed, showing (RR 0.95, 95% 0.76-1.19) for dementia in relation to fish consumption (Devore *et al.,* 2009). The pooled data of RR between short and long-term follow up studies were similar (Table 6.2).

6.6.6 Is there an exposure-response relationship?

An exposure-response relationship was identified between different levels of fish consumption and risks of dementia and AD in our meta-analysis. The majority of identified studies (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005; Schaefer *et al.,* 2006; Barberger-Gateau *et al.,* 2007; Albanese *et al.,* 2009; Devore *et al.,* 2009; Kim *et al.,* 2010; Lopez, Kritz-Silverstein and Barrett-Connor, 2011) showed this, with non-statistical significance. Morris *et al.* (2003) demonstrated a non-significant dose-response relationship of AD with fish consumption; (RR 0.6, 95% 0.3-1.3) in participants who consumed fish 1-3 times monthly, (RR 0.4, 95% 0.2-0.9) in those who consumed fish once weekly and RR 0.4, 95% 0.2-0.9) in ≥ twice weekly (trend p=0.07). However, other cohort studies (Barberger-Gateau *et al.,* 2002; Schaefer *et al.,* 2006; Barberger-Gateau *et al.,* 2007) showed that the reduced risk of dementia was not significant in the highest level of fish consumption. This may be due to the small number of patients in these groups. Nevertheless, the pooled data in this meta-analysis (Table 6.3) across all the different levels of fish intake from the included studies have shown a significant reduction in the risk of dementia (Fig. 6.5) and AD.

6.6.7 Is the association biologically plausible?

The biological mechanism exhibited by fish consumption in relation to the prevention of dementia may result from the presence of omega-3 fatty acids as part of their constituents. Omega-3 fatty acids are a major component of neuronal membranes, with cardio-protective, anti-inflammatory, antioxidant and anti-atherogenic properties (Calder, 2006; Uauy and Dangour, 2006; Innis, 2007). They have the capability to display a beneficial effect on the risk of developing dementia and AD, particularly vascular dementia (Kalmijn *et al.,* 1997; Engelhart *et al.,* 2002; Barberger-Gateau *et al.,* 2007). Fish is a beneficial source of essential amino acids, micronutrients and vitamins, thus increasing the protective effect they exhibit on the risk of developing all-cause dementia and cognitive impairment (Chandra, 2001). Fatty fish are known to be richer sources of DHA and EPA, which are naturally found in trout, tuna, salmon, sardines, herring (Mohanty *et al.,* 2016), and mackerel, but minimal sources are found in lean fishes, such as cod, haddock, and halibut. An increase in the intake of fatty fish may also be positively associated with a decrease in the level of the consumption of saturated fat, thus reducing the risk of stroke (Larsson *et al.,* 2011). This might be as a result of the anti-inflammatory, antithrombotic, antioxidant and anti-amyloid properties of its omega-3 fatty acid components (Calder, 2006; Connor and Connor, 2007; Innis, 2007).

6.6.8 Is the evidence coherent with knowledge of the natural history of disease?

Dietary fatty acid has displayed a significant effect on the risk of developing CVD (Connor, 2000; Nestel, 2000; Connor and Connor, 2007) depression (Grosso *et al.,* 2016) and in children's cognitive impairment (Eilander *et al.,* 2007; Gould, Smithers and Makrides, 2013). This association involves the higher consumption of saturated fat and cholesterol and lower consumption of PUFA (omega-3 fatty acids). Intake of omega-3 fatty acids has been associated with reduced risk of cognitive impairment and dementia through several possible mechanisms. They display a cardio-protective property that makes them protective over several cardiovascular risk factors such as stroke, atherosclerosis and inflammation through influence on brain development and proper membrane function (Kalmijn *et al.*, 1997; Huang, 2010). They have exhibited their cognitive-enhancing effect during infancy, childhood, old age and among adults with neurocognitive impairments in some clinical trials (Huang, 2010; Luchtman and Song, 2013). This beneficial effect was supported by the outcome of the Chicago Health and Aging 6-year prospective cohort study (CHAP) that involved fish intake and cognitive impairment (Morris *et al.*, 2005), and in the result revealed in the Zutphen Elderly 5-year prospective cohort study of fish consumption, omega-3 fatty acids and cognitive decline (van Gelder *et al.*, 2007). The China Health and Nutrition Survey also maintained that an adequate intake of fish does lower cognitive decline (Qin *et al.*, 2014).

6.6.9 Is there experimental evidence?

Numerous animal studies have demonstrated the positive role that omega-3 fatty acids (a fish constituent) play on brain development. They increase neurotransmission (Horrocks and Farooqui, 2004), enhance memory capabilities (Hashimoto *et al.*, 2005), enhance the excitability regulation of neuronal membranes (Xiao and Li, 1999), decrease neurons ischemic damage (Okada *et al.*, 1996) and increase the cerebral flow of blood (Tsukada *et al.*, 2000). Experimental studies showed that rats that had a reduced level of DHA in their diet exhibited an impaired cognitive function, while those animals that had a prolonged administration of DHA demonstrated an enhanced gain in memory (Gamoh *et al.*, 1999). These studies confirmed that the exposure of animal models to the intake of DHA positively influenced their neurological status.

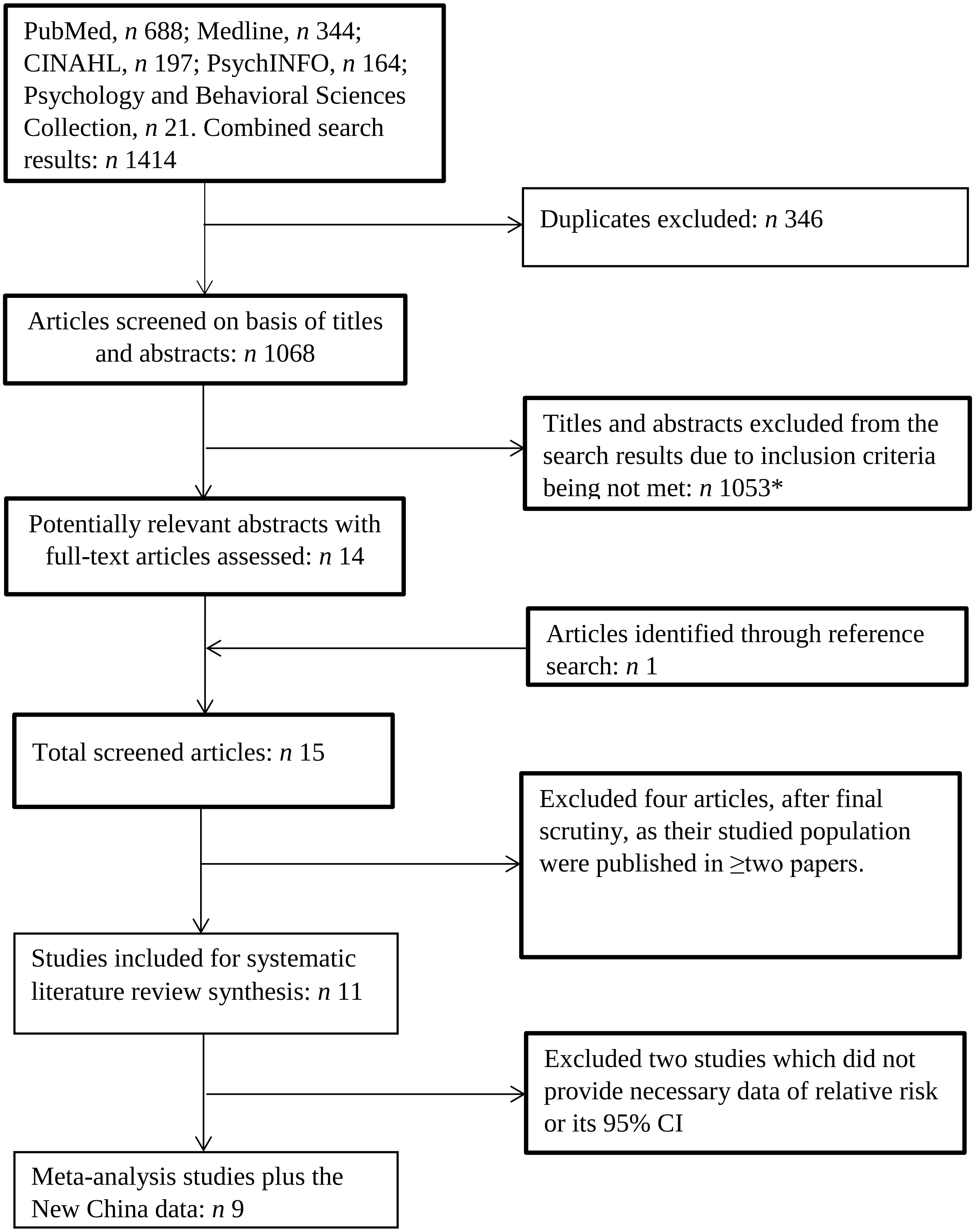
6.6.10 Does the evidence accord by analogy with that from other fields?

Previous studies showed a significant beneficial effect of intake of omega-3 fatty acids as a supplement on dementia and cognitive impairment (Morris *et al.,* 2005; van Gelder *et al.,* 2007). Findings from a randomized control trial (RCT) that involved supplementing the treatment group with arachidonic acid and DHA, components of fish fatty acids, did exhibit a significant beneficial effect on cognitive function in the treatment MCI group, while the placebo group showed no significant beneficial effect (Kotani *et al.,* 2006). A similar beneficial effect was observed among an MCI group in an RCT of forty-six participants of (twenty-three with mild or moderate AD and twenty-three with MCI) who were randomised to receive either an omega-3 PUFA treatment or olive-oil (placebo) (Chiu *et al.,* 2008). In a 1-year RCT that investigated the effects of fish oil supplementation on cognitive function in older adults, Lee *et al.* (2013) found a significant beneficial effect within a short-term and after a 12 month period on participants' working memory, immediate verbal memory and in the delayed recall ability among the treatment group that were supplemented with fish oil. The results of the current study are thus consistent with the findings of these studies, thereby acknowledging the positive influence that fish and its constituents has on cognitive function.

6.7 Implication and conclusion of the study findings

This Chapter study demonstrated a significant beneficial effect of eating fish on reducing dementia. The epidemic of dementia has become a public health problem worldwide. As the world population is continuing to age, the number of people with dementia will continue to rise. The vast majority of the increment is expected to be in LMIC, which currently hold 58% of people living with dementia, with further increment by the year 2050 (Prince *et al.,* 2015). In China, there is a growing number of people living with dementia due to the population of older people with mixed characteristics (e.g. low level of education but rapidly increased income) (Chen *et al.*, 2012). Our study demonstrated a significant association of higher fish consumption with reduced risk of dementia, which further indicates the potential importance of consuming fish in preventing dementia worldwide. At present, global per capita fish consumption is estimated to be on average 20 kg/year (FAO, 2016), and is lower in LMIC (18.8 kg/year) than in high-income countries (26.8kg/year). Our study demonstrated consistent findings of the impact of fish consumption on the risk of dementia between LMIC and high-income countries. People should thus increase their level of fish consumption, especially in areas where the consumption is quite low such as LMIC, to reduce the burden of dementia. Also, people living in high income countries, including the UK, should be informed of the beneficial impact of fish consumption to increase its intake further.

Figure 6.1: Flowchart showing the literature search technique



*Reasons for exclusions: appropriate outcome not reported, randomized control trial; assessed another exposure other than fish; assessed another outcome other than dementia or Alzheimer's disease; articles on importance of fish to dementia and brain development; news briefs, articles on elderly nutrition; literature review/meta-analysis; presentation.

Figure 6.2: Forest plot for the pooled relative risk (RR) of fish consumption and dementia* risk

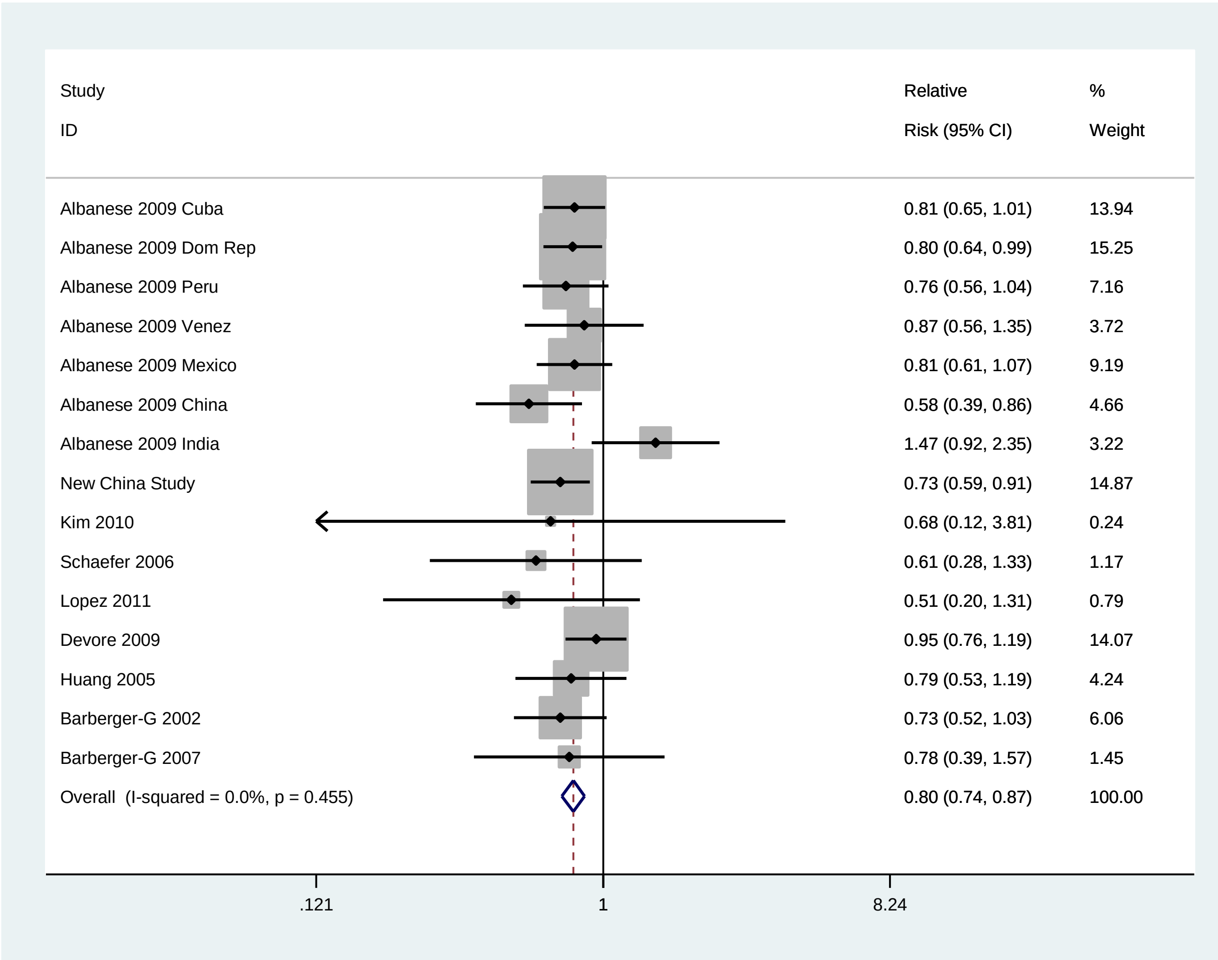


Fig. 6.2 Forest plot for the pooled relative risk (RR) of fish consumption and dementia* risk. The study-specific RR and 95% CI are represented by the black diamond and the horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis. The centre of the open diamond and the vertical dashed line represent the pooled RR and the width of the open diamond represents the pooled 95% CI. *One of the nine studies used for the meta-analysis (Morris *et al*., 2003) provided the RR result for Alzheimer's disease only and therefore it was not included in the above analysis.

Figure 6.3: Forest plot for the pooled relative risk (RR) of fish consumption and AD risk

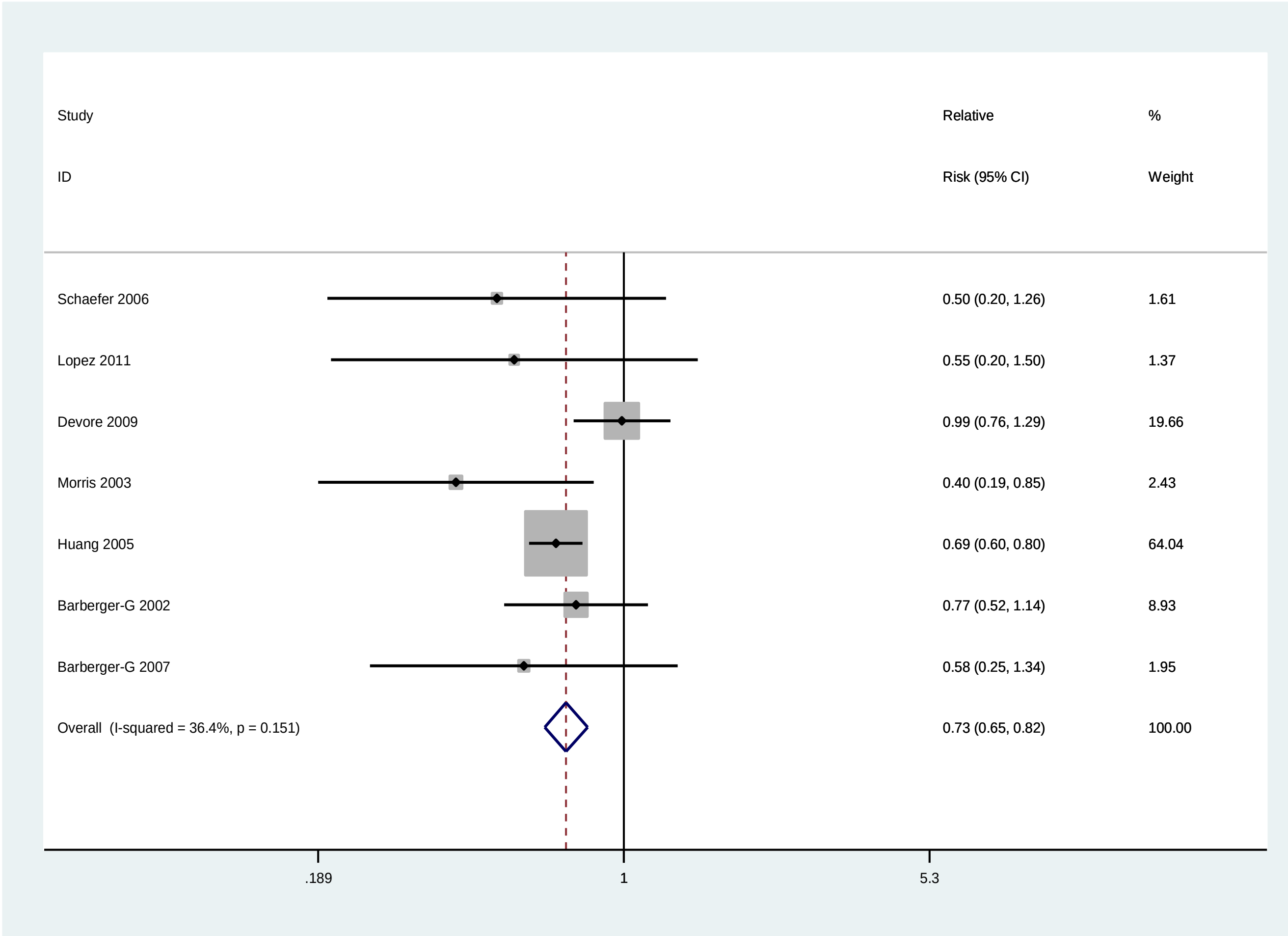


Fig. 6.3 Forest plot for the pooled relative risk (RR) of fish consumption and Alzheimer's disease risk. The study-specific RR and 95% CI are represented by the black diamond and the horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis. The centre of the open diamond and the vertical dashed line represent the pooled RR and the width of the open diamond represents the pooled 95% CI.

Table 6.1: Numbers, percentages and OR (with 95% CI) for dementia according to level of fish consumption: the six-province health survey in China conducted among 6981 Chinese adults aged ≥60 years, 2007-2011

Frequency of fish consumed over the past 2 years	**Dementia**					**Multivariate adjusted analysis**		
	No		Yes					
	n	(%)	n	(%)	*P**	OR†	95%CI	*P*
Fish								
No	1438	94.1	90	5.9	<0.001	Ref.		
Once weekly	2516	95.6	115	4.4		0.79	(0.49-1.29)	0.355
> Twice weekly	1875	96.7	63	3.3		0.59	(0.38-0.90)	0.014
≥once daily	826	93.4	58	6.6		0.76	(0.55-1.04)	0.089
Total	6655	95.3	326	4.7				

* P value from Chi-square test.

†Adjusted for age, sex, province, urban-rural areas, education level, smoking status and stroke.

Table 6.2: Pooled analysis results for dementia risk in people with fish consumption versus those with no or lower levels of fish consumption, by study design, level of fish consumption and country of study in terms of income

Variable for subgroup data analysis	No. of studies	No. of studied populations	No. of Participants	No. of dementia	RR (95% CI)
By study design					
Cross-sectional studies*	2	8	21,937	1671	0.79 (0.72-0.88)
Prospective cohort studies (follow up ≤ 5 years)	2	2	8,327	323	0.67 (0.38-1.18)
Prospective cohort studies (follow up >5 years)	4	4	9,532	1,112	0.85 (0.72-1.00)
By level of fish consumption §					
Continuous*	9	15	39,853	3,139	0.80 (0.74-0.87)
Only two levels	1	1	488	99	0.61(0.28-1.33)
Only three levels	4	4	7,110	710	0.86 (0.71-1.03)
Four levels *	3	3	17,299	985	0.77 (0.61-0.98)
By country of study in terms of income					
High income countries	7	7	17,916	1,468	0.83(0.71- 0.97)
Low and middle income and the six-province study in China	2	8	21,937	1,671	0.79 (0.72 -0.88)

CI: Confidence Interval; RR: Relative Risk.

*including the new community-based cross-sectional study of the six-province health survey in China

§ fish consumption level: “Continuous” means that the authors analysed data of fish consumption for the results presentation; “Only two levels” means that the authors analysed the data of fish consumption in two levels, based on the questionnaire record or grouping them into two; “Only three levels” means that the authors analysed the data of fish consumption in three levels; and “four levels” means that the authors analysed the data of fish consumption in four levels.

Table 6.3: Dose-response relationship between fish consumption and risk of dementia and AD †

Consumption of Fish	Dementia				AD			
	No. of Studies *	No. of Participants	No. of dementia	RR (95% CI)	No. of Studies	No. of Participants	No. of AD cases	RR (95% CI)
Low level	6 §	23,239	1582	0.84 (0.72-0.98)	6	18,432	1,075	0.88 (0.74-1.04)
Middle level	7 §	24,409	1695	0.78 (0.68-0.90)	5	16,770	899	0.79 (0.65-0.96)
High level	3§	17,299	985	0.77 (0.61-0.98)	3	11,133	504	0.67 (0.58-0.78)

Abbreviations: CI: Confidence Interval; RR: Relative Risk.

† Each of these low, middle and high levels of fish consumption *v.* no or lowest consumption of fish.

*The same number of studied populations

§Including the new community-based cross-sectional study of the six-province health survey in China

Table 6.4: The pooled analysis of AD risk in people with fish consumption versus those with no or lower level of fish consumption, by study design and by study design, level of fish consumption and country of study in terms of income

Variable for subgroup data analysis	Nos of studies*	Participants	Nos of Alzheimer's Dis	RR (95% CI)
By study design				
Prospective cohort studies (follow up ≤ 5 years)	3	9,142	344	0.49 (0.30-0.80)
Prospective cohort studies (follow up year >5 years)	4	9,532	761	0.75 (0.66-0.84)
By fish consumption level				
Continuous	7	18,674	1105	0.73 (0.65-0.82)
Only 2 levels	2	1,904	206	0.72 (0.50-1.03)
Only 3 levels	2	5,637	395	0.95 (0.74-1.23)
4 levels	3	11,133	504	0.67 (0.58-0.78)
By country of study in terms of income				
High income countries	7	18,674	1105	0.73 (0.65-0.82)
LMICs	0	NA	NA	NA

Abbreviations: Confidence Interval-CI; Relative Risk-RR.

*The same number of studied populations

Figure 6.4: Funnel plot for the publication bias in the analysis of all dementia cases

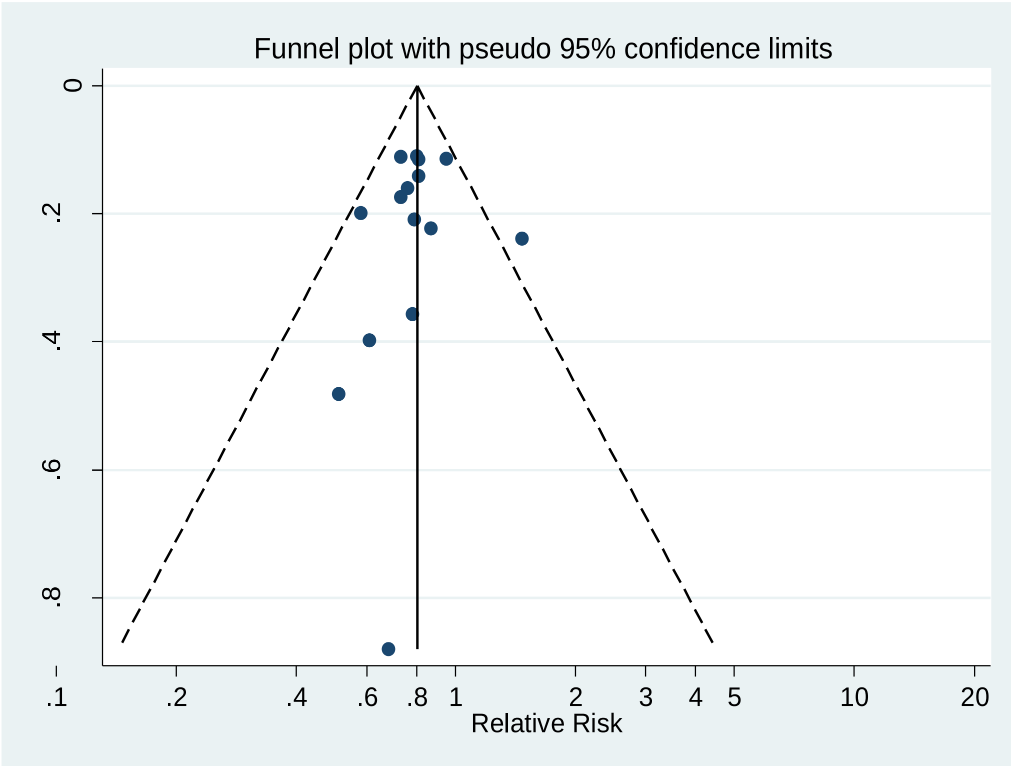


Figure 6.5: Forest plot for the pooled relative risk (RR) of the combination of all the fish consumption levels and dementia risk

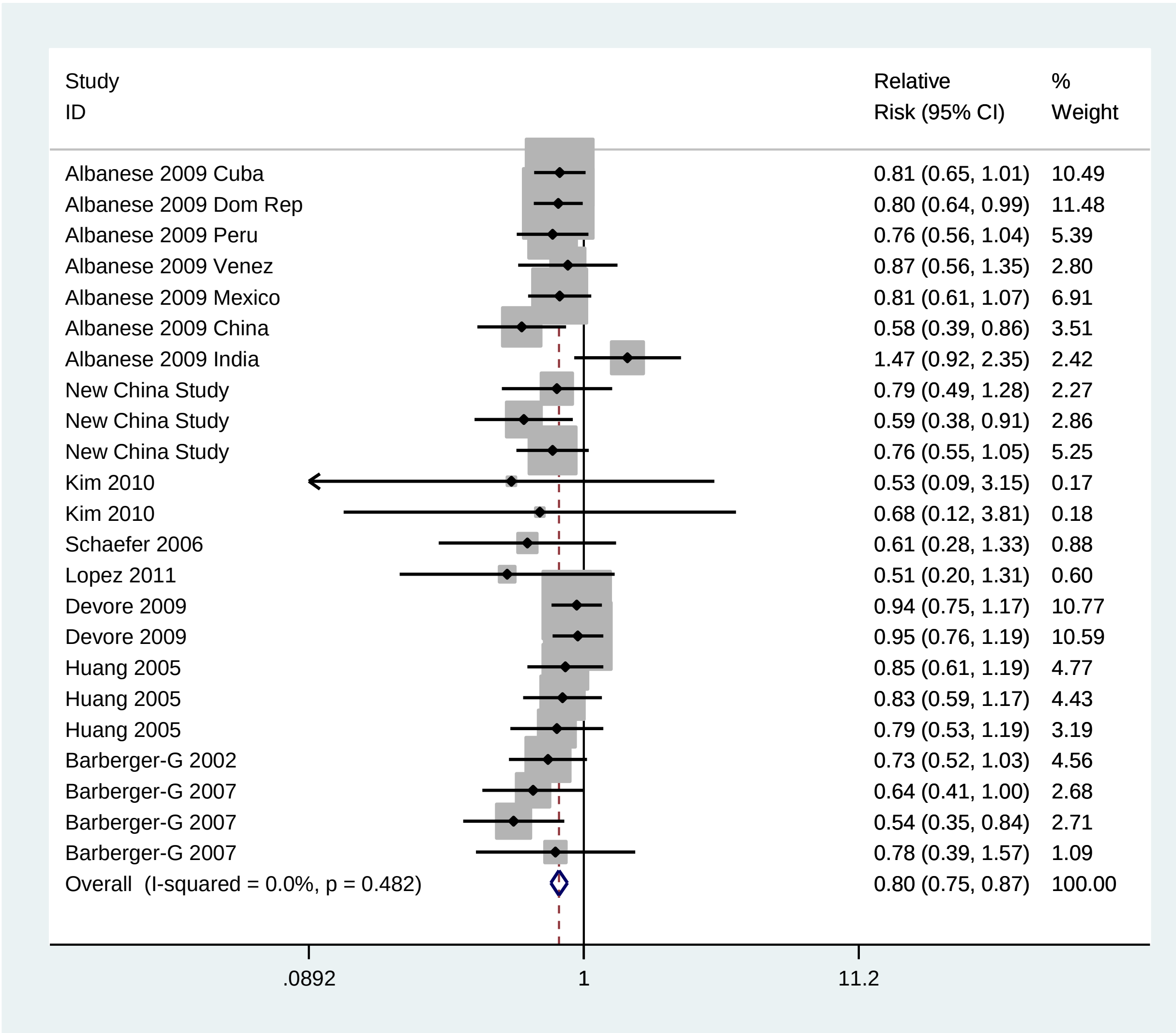


Fig. 6.5 Forest plot for the pooled relative risk (RR) of the combination of all the fish consumption levels and dementia risk. The study-specific RR and 95% CI are represented by the black diamond and the horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis. The centre of the open diamond and the vertical dashed line represent the pooled RR and the width of the open diamond represents the pooled 95% CI.

CHAPTER SEVEN: IMPACT OF FISH CONSUMPTION ON INCIDENT DEMENTIA: THE FOUR-PROVINCE COHORT STUDY

7.1 Introduction

As the world population ages, there are more people living with dementia and the burden of dementia is expected to significantly increase in future (Prince *et al.*, 2015). There is increasing evidence on the role nutrition particularly fish consumption plays in delaying or preventing the risk of dementia. Fish is the major source of long-chain omega-3 polyunsaturated fatty acids (PUFAs) with various essential nutrients (Wallin *et al.*, 2012; Lund, 2013). Fish consumption has contributed immensely to the prevention of non-communicable chronic diseases over the years (Xun *et al.,* 2011; Zheng *et al.*, 2012), because of its long chain omega-3 polyunsaturated fatty acids (PUFAs) constituent that comprises of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Salem *et al.,* 2001). These fatty acids are important constituents for proper brain functioning and neurocognitive development (Connor, 2000; Salem *et al.*, 2001). Although there has been an increase in epidemiological studies on the role of fish consumption in the prevention of dementia, but the findings are inconsistent (Morris *et al.*, 2005; van Gelder *et al.,* 2007). Some studies suggested an association between fish consumption and the risk of dementia (Kalmijn *et al.,* 1997; Barberger-Gateau *et al.*, 2002; Morris *et al.*, 2003), while others showed no association (Engelhart *et al.*, 2002).

Previous studies on fish consumption and dementia are predominately from high income countries, where the population characteristics make it difficult to deal with confounding effects including high levels of cardiovascular diseases and risk factors on the association between fish consumption and dementia risk and the findings could not be generalised to other countries. There is limited data (Zhang *et al.,* 2016) from low- and middle-income countries (LMIC), where people have high risk of dementia but low level of fish consumption (Prince *et al.,* 2015).

In Chapter 6 above, we found a significant association of fish consumption with dementia risk in the cross-sectional data. In this Chapter, I analysed the data of a population-based cohort study to examine the impact of fish consumption on incident dementia in older people, and to examine the gender differences in the impact. I also performed a meta-analysis using the findings from the cohort studies to identify the impact of fish consumption on incident dementia.

7.2 Methods

7.2.1 Study Participants

The study population was derived from the four-province study. In 2008-2009, we selected one rural and one urban community from each of the four provinces (Guangdong, Heilongjiang, Shanghai, Shanxi) as the study fields. We tried to recruit no fewer than 500 participants in each community and employed a cluster randomised sampling method to choose residential communities (the district in urban areas and the village in rural) from each of the four provinces. The target population consisted of residents aged ≥60 years living in the area for at least 5 years. Based on the residency list of the committees of the village and the district, we recruited a total of 4314 participants with an overall response rate of 93.8%. The local survey team interviewed the participants at home. The main interview included a general health and risk factors record, the Geriatric Mental State (GMS) questionnaire (Copeland *et al.,* 2002) and other components of the 10/66 algorithm dementia research package (Prince *et al.,* 2003). We carried out a two-phase interview to save our research resources. In phase one, we completed the general health and risk factors record, the GMS, the Community Screening Instrument for Dementia (CSI-D) cognitive test and Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Using three of the four constituent components of the 10/66 algorithm (i.e. data of GMS-AGECAT, the CSI-D cognitive test and CERAD interview), we calculated a probability of possible dementia for each participant. In phase two, we selected the top 15% of the population who had the highest probability of having "dementia" as "probable cases" and a random sample of 5% of the rest as "probable non-cases" for subsequent interviews in each province. The interview team completed the CSI-D informant interview for the selected participants.

7.2.2 Risk factors

In the general health and risk factors questionnaire interview, details relating to socio-demography including educational level, occupational class, level of income, lifestyle, social networks and support, histories of chronic diseases and risk factors were recorded (Chen *et al.,* 2005). We measured height, weight, waist circumference and blood pressure for all participants. In the interview, information about each participant dietary intake was collected. These include rice, wheat flour, meat, fish, egg, fresh vegetable, fruit, chilli pepper, garlic, ginger and different types of vegetable oils. Participants' frequency of fish intake in the past two years was recorded as (1) Never eat, (2) ≤Once a week, (3) >Once a week and < Daily, (4) Once a day, and (5) ≥ Twice a day.

7.2.3 Diagnosis of dementia at baseline

We employed the 10/66 dementia algorithm to diagnose dementia, which included the data from the GMS-AGECAT diagnostic output, the CSI-D, COGSCORE, the CSI-D informant interview (RELSCORE), and the CERAD ten-word list learning task with delayed recall (Prince *et al.*, 2003;

Prince *et al.,* 2008). We used a cut-off point of probability (≥0.25) derived from the full 10/66 algorithm to diagnose dementia, which has been validated in China (Rodriguez *et al.,* 2008).

7.2.4 Follow up of the cohort

In 2011-2012, using the same interview materials at baseline, we successfully interviewed 2892 surviving cohort members (wave 2) after identifying 259 deaths in the follow up. We used the 10/66 dementia algorithm to diagnose new cases of dementia.

7.3 Data Analysis

Of 4134 participants, after excluding those who did not report consumption of fish or had dementia diagnosed at baseline, we analysed data of 2770 participants who were followed up. We examined the distributions of the baseline socio-demographic and clinical characteristics of participants with different levels of fish consumption documented at Wave 2 survey using chi-squared test for categorical variables and one-way analysis of variance for continuous outcome variables. The person-years at risk for each of the participants were computed from the beginning of the study. The incidence dementia rate per 1000 person-years was also computed for each level of fish consumption. A multivariate adjusted binary logistic regression models was employed to assess the risk of incident dementia in relation to any levels of fish consumption over the past two years. We computed the odds ratio (OR) and 95% confidence intervals of each fish consumption levels associated with incident dementia over a follow up period of 3-years. Five models were computed for the variables that might mediate the association of fish consumption and incident dementia. To increase the statistical power, we combined two of the fish consumptions levels ("never eat" or "once a week") into one due to small sample sizes. In the first model, we adjusted for age (cont.), sex, province, rural-urban and educational level by taking the combination of "never eat with once a week" fish consumption levels as the reference category. In the second model, further adjustment was made for body mass index (BMI), smoking status, and alcohol consumption. In the third model, further adjustment was made for marital status, frequency of visiting children or other relatives, hypertension (yes or no), diabetes, heart disease, stroke, activity of daily living and depression, cancer in addition to all the variables in the previous model. In the fourth model, an additional adjustment was made for meat and egg consumption plus all the variables in the previous models. Finally, in the fully adjusted model, additional adjustment was made for vegetable and fruit plus all the variables in model 4. We further examined gender differences in the impact by performing separate data analysis on men and women in the final regression model. All data analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL). P values <0.05 were considered statistically significant.

7.4 Meta-analysis

Data (Odds ratios (ORs), Rate ratios or Hazard ratios (HRs) and their 95% CIs) were pooled from published studies and the four provinces cohort study. All these measures and their 95% CIs were pooled together as a relative risk (RR) with the assumption of achieving a common unit of comparison. We analysed the data grouped by studied population in each of the study which we selected to investigate all types of dementia in relation to fish consumption. The studied population was defined as each individual sample in the study according to its place (country, regions), time (years) and person (e.g. ethnicity) where applicable. A random effect model was employed if the heterogeneity of the within and between studies variation were significant; otherwise, a fixed effect model was used. Publication bias was evaluated using the Egger's regression (Egger *et al.,* 1997). First, we tried to assess an overall RR of dementia in participants who consumed fish in comparison with those who did not. If the article only gave the RRs in different levels of fish consumption, we took the figure from the highest fish consumption group for analysis. If the article only gave the figures from the continuous data analysis of fish consumption or from only high vs low levels of fish consumption, we took them in the meta-analysis. We repeated above analyses for AD, where the data were available. All analyses were performed using the statistical software package STATA version 14.2.

7.4 Results

7.4.1 Chinese Cohort: The four-provinces study

Of 2892 participants, 2770 (95.8%) responded to the fish consumption questionnaire. In the cohort of 2770 participants, 249 new cases of dementia were documented over a follow-up period of 3 years (8692.29 person-years). The participants' average age (SD) was 70.3 (6.85) years, and 56.2 % were women. A total of 654 (23.6%) participants "never" consumed fish over the past two years, 789 (28.5%) consumed fish "once a week", 861 (31.1%) consumed fish "more than twice a week", and 466 (16.8%) consumed fish ≥once a day. Table 7.1 shows the numbers and percentages of the socio-demographic and clinical characteristics of the study participants in each of the four fish consumption levels. Participants with increased consumption of fish were significantly more likely to be older, have never smoked and drank alcohol, living in urban area, high educational level, occupational class and income. Increased fish consumption was significantly associated with being currently married, frequently visiting children/relatives, and having normal blood pressure, no heart disease and dementia and activity of daily living (ADL) score (0-≥5). In addition, participants with increased consumption of fish were significantly more likely to consume meat, egg, fresh vegetables, and fruits. There were no significant differences in living with others and having no diabetes and depression across the four fish consumption levels.

Table 7.2 shows the total person-years, incidence of dementia, and the multivariate adjusted ORs of dementia and 95% CIs of different levels of fish consumption compared with (“never eat” or “once a week”). In the multivariate adjusted analysis, a non-significant reduction in the risk of dementia was found when the highest (≥once a day) and the moderate (more than twice a week) fish consumption levels were compared to the lowest fish consumption level (never eat and once a week). Similarly, non-significant association of the highest and the moderate fish consumption levels with risk of dementia was found when further adjustment was made in the 2nd and the 3rd model. The non-significant reduction was maintained in the 4th model after additional adjustment with dietary variables, but with slight increase in odds ratio, when the highest fish consumption level (≥once a day) was compared to those that consumed fish at (“never eat” or “once a week”). The final model 5 showed a 17% non-significant reduction in the risk of dementia (adjusted OR 0.83, 95% CI 0.47-1.49) among the participants that consumed fish (≥Once a day) when compared to those that consumed fish (“never eat” or “once a week”), while no association was found among those that consume fish (More than twice a week).

Table 7.3 shows the total person-years, incidence of dementia, and the multivariate adjusted ORs of dementia and 95% CIs of different levels of fish consumption compared with (“never eat” or “once a week”) in men and women respectively. The multivariate adjusted analysis models show a non-significant reduction in the risk of dementia among the male participants when the fish consumption levels “≥once a day” and “More than twice a week” were compared with fish consumption levels (“never eat” or “once a week”) (OR 0.67, 0.23-1.90) and 0.55 (0.17-1.81) respectively. However, no association was found among the female participants, when the highest and the moderate fish consumption levels "≥once a day" and "More than twice a week" were compared with fish consumption levels ("never eat" or "once a week").

7.4.2 Meta-analysis

The findings of the four provinces cohort study in China above were pooled together with those of nine published cohort studies (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005; Schaefer *et al.,* 2006; Devore *et al.,* 2009; Lopez, Kritz-Silverstein and Barrett-Connor, 2011; Fischer *et al.,* 2018; Ngabirano *et al.,* 2019; Tsurumaki *et al.,* 2019) to assess the impact of fish consumption on the risk of dementia in the world. In total, 3183 dementia cases in 35017 participants were analysed. Data from these cohort studies suggested little variability in the associated effects between studies. The fixed effect model analysis showed that there was a 15% significant reduction in the risk of dementia in participants who consumed fish (or consumed fish at a higher level) compared to those who did not eat fish (or who consumed fish at a lower level) (see Figure 7.1). There was little evidence of publication bias; the Egger method of bias estimate showed a p-value of 0.276.

In all eight studies which examined the risk of AD specifically in relation to fish consumption (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005; Schaefer *et al.,* 2006; Devore *et al.,* 2009; Lopez, Kritz-Silverstein and Barrett-Connor, 2011; Fischer *et al.,* 2018; Ngabirano *et al.,* 2019), the pooled data (in total 1806 cases of AD) showed a significant impact of fish consumption on reduced risk of AD (RR 0.80, 95% CI 0.66-0.98; the forest plot is shown in Figure 7.2). All studies were undertaken in high income countries and were of cohort design.

Figure 7.1: Forest plot for the pooled relative risk (RR) of fish consumption and dementia* risk

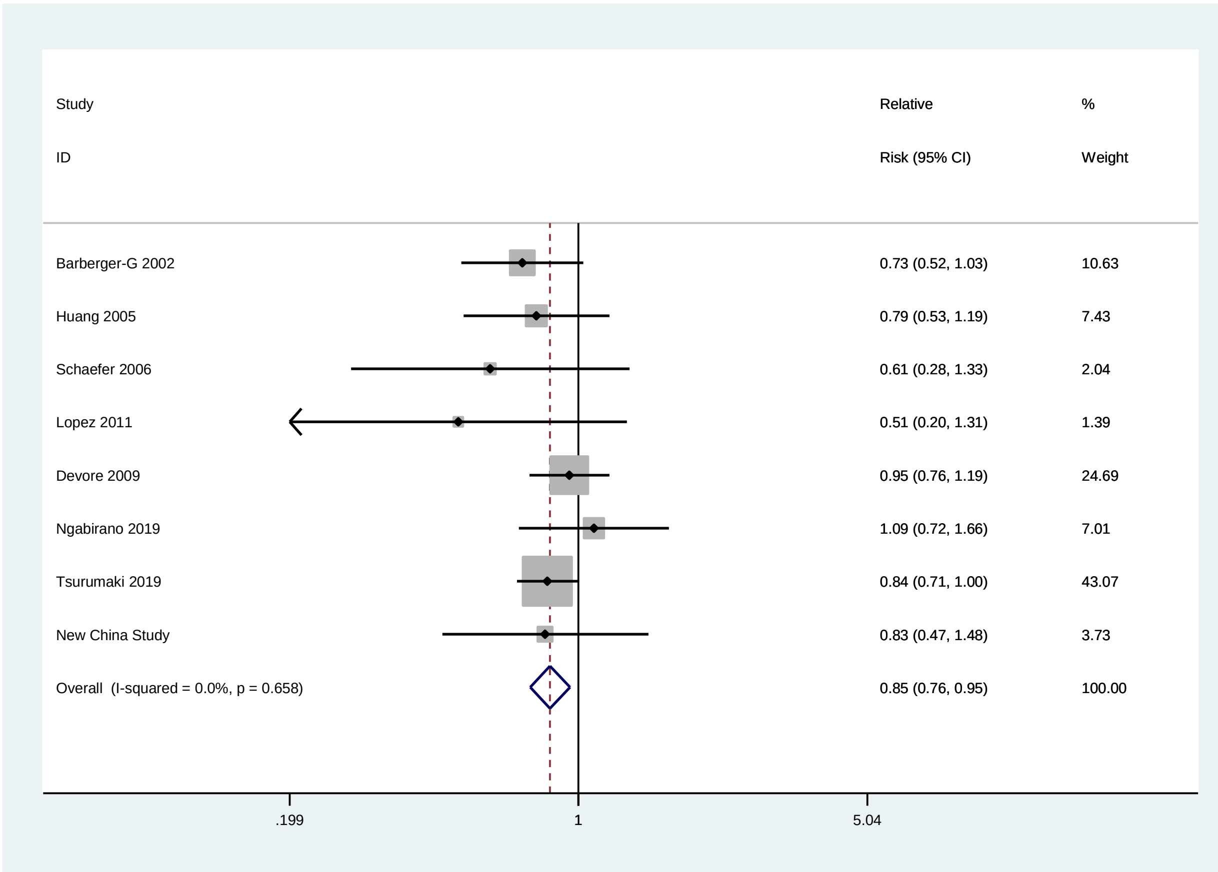


Fig 7.1. Forest plot for the pooled relative risk (RR) of fish consumption and dementia* risk. The study-specific RR and 95% CI are represented by the black diamond and the horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis. The centre of the open diamond and the vertical dashed line represent the pooled RR and the width of the open diamond represents the pooled 95% CI. *Two of the nine studies used for the meta-analysis (Morris *et al*., 2003; Fischer *et al*., 2018) provided the RR result for Alzheimer’s disease only and therefore it was not included in the above analysis.

Figure 7.2: Forest plot for the pooled relative risk (RR) of fish consumption and AD risk

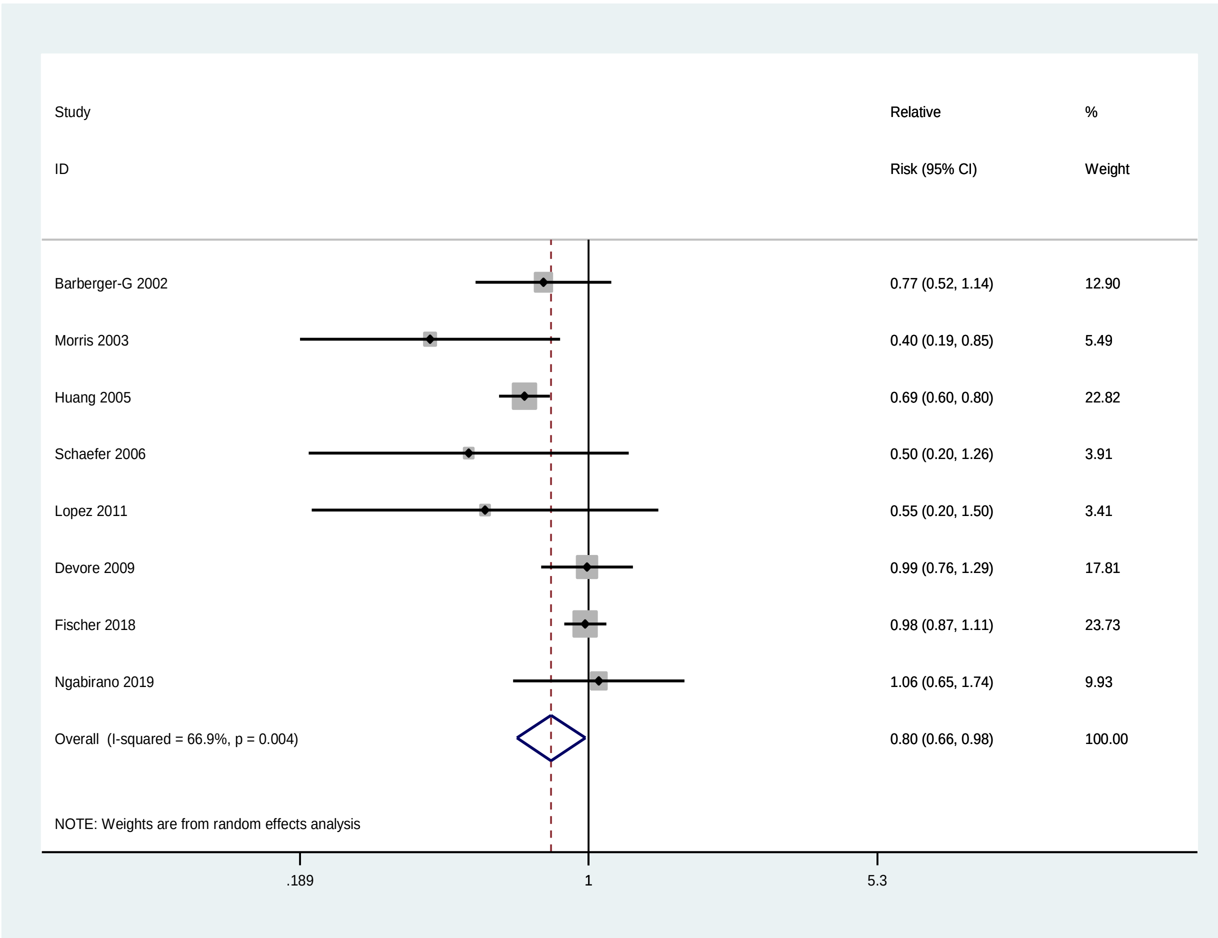


Fig 7.2. Forest plot for the pooled relative risk (RR) of fish consumption and Alzheimer's disease risk. The study-specific RR and 95% CI are represented by the black diamond and the horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis. The centre of the open diamond and the vertical dashed line represent the pooled RR and the width of the open diamond represents the pooled 95% CI.

7.5 Discussion

This population-based cohort study among older people in China examined the association of fish consumption and incident dementia in older people, and the gender differences in the association. The result revealed a non-significant inverse association of higher fish consumption and the risk of dementia in older people. A non-significant reduced risk of dementia was found among the men with higher fish consumption over the past two years, but this was not found among the women.

The overall finding of the inverse association of fish consumption and the risk of dementia found in this study is consistent with those in previous studies. The Rotterdam population-based cohort study of 5,386 participants aged ≥55 years with a mean follow-up period of 2.1 years and 58 dementia cases revealed a reduction in the risk of dementia when the highest fish consumption level of >18.5g/day was compared with the lowest fish consumption level of ≤3.0g/day (adjusted OR 0.40, 95% CI 0.20-0.90) (Kalmijn *et al.,* 1997). Similarly, a Chicago health and aging US cohort study of 815 participants aged 65-94 years with 131 AD cases and a follow up period of 3.9 years found a 60% significant reduction in the risk of AD when the highest fish consumption "≥1/week" level was compared to the lowest fish consumption level of "rarely or never" (RR 0.40, 95% CI 0.20-0.90) (Morris *et al.,* 2003). In a US cohort study of 2,233 participants aged ≥65 years and 5.4 years follow-up period, Huang *et al.* (2005) found a 35% significant reduction in the risk of dementia among participants that consumed fatty fish ≥4times/week when compared to those that ate fish <once/month. Conversely no beneficial effect was found among those that consumed lean fried fish (Huang *et al.,* 2005). In contrast, the PAQUID (Personnes Agées QUID) cohort study of 1416 French participants aged ≥68 years with a follow-up period of 7 years and 170 dementia cases found a non-significant reduction in the risk of dementia among participants that consumed fish or seafood at least once a week (HR 0.73, 0.52-1.03) (Barberger-Gateau *et al.*,

2002). Likewise, a French cohort study of 8,085 non-demented participants aged ≥65 years with a 4-year follow-up period and 281 incident dementia cases found a non-significant reduction in the risk of dementia among participants that consumed fish ≥4times/week (HR 0.81, 0.45-1.46) when compared with never or <1/week (Barberger-Gateau *et al.*, 2007).

A Dutch cohort study of 5395 participants aged ≥55 years with mean follow-up period of 9.6 years and 465 dementia cases found no impact of increased fish consumption on the association between the risk of dementia (HR 0.95, 95% CI 0.76-1.19) in comparison with those who never ate fish (Devore e*t al* 2009). Similarly, a recently published Three-City cohort study of 5934 participants aged ≥65 years with a mean follow-up period of 9.8 years and 662 dementia cases also found no significant association of fish consumption with dementia (HR 1.09, 0.72-1.67) and AD (1.06, 0.65-1.75), when the highest fish consumption frequency of ≥4 times/week was compared with the lowest frequency of consumption of <1 time/week (Ngabirano *et al.*, 2019). The variation in the findings of these studies and our studies could be explained by the possible existence of reverse causation, which arises when the occurrence of disease affects and changes the food consumption habits of individuals consequentially causing a poorer diet with reduced fish intake. It could also be that the dietary information collected at baseline may not represent the dietary consumption over a longer follow-up period. Also, it could be due to the variation in the studies sample sizes, the length of follow-up, the type of fish assessed, the fish preparation method, attrition rate, selection bias and the adjusted confounding variables in each of the studies.

The current study exhibited gender differences on the association of fish consumption and the risk of dementia. There are a limited number of studies investigating the impact of gender disparity on the association of incident dementia and fish consumption. A study published in 2019 on the association of meat, fish, fruits and vegetables on the risk of long-term dementia and AD reported a gender difference on meat and vegetable consumption on dementia risk but failed to report the gender difference on fish consumption and dementia risk (Ngabirano *et al.*, 2019). Another recently published Japanese Ohsaki cohort study of 13 102 participants aged ≥65 years with a follow-up period of 5.7 years and 1118 dementia cases found a borderline significant inverse association of fish consumption and the risk of dementia for both male and female, when the highest quartile of fish consumption (HR 0.82, 0.64-1.06) and 0.87 (0.69-1.09) and the moderate quartile of fish consumption (HR 0.84, 0.65-1.08) and 0.88 (0.72-1.08) respectively was compared with the lowest quartile of fish consumption (Tsurumaki *et al.*, 2019). However, our cohort study showed a non-significant association when the highest and moderate fish consumption levels were compared with the lowest fish consumption level among the male participants and no and increased association was found among the female participants. Due to the inconsistency in the results, further research is required to elucidate the impact of gender differences on the association of fish consumption and the risk of incident dementia.

The meta-analysis findings in this study are biologically plausible due to the presence of omega-3 PUFA constituents in fish (Uauy and Dangour, 2006; Connor and Connor, 2007). In addition to playing a role in the composition of neuron membrane, brain development and functioning (Bourte *et al.*, 1989; Salem *et al.*, 2001), fish and its omega-3 PUFA constituents also have beneficial effect on some non-communicable diseases e.g. CVD, thereby reducing the risk of dementia. This was demonstrated through their anti-inflammatory properties (Calder, 2013), which involve inhibiting and reducing the production of proinflammatory cytokines in humans (Blok, Katan and van der Meer, 1996). Omega-3 PUFA also improves the endothelial function and blood flow to the brain (Tsukada *et al.*, 2000; Wang *et al.*, 2012). They also modulate cellular metabolic functions and the expression of genes (Jump, 2002; Seo *et al.*, 2005; Cederholm *et al.*, 2013).

7.5.1 Strengths and Limitations of the study

The main strength of this study is its prospective cohort design, its large sample size (benefited from pooling data) and the long-term follow-up period. Also, the detailed confounding variables available that allowed us to comprehensively explore the role of fish consumption could have possibly influenced the association of fish with the risk of dementia. Older Chinese population have higher levels of socioeconomic deprivation, but low levels of cardiovascular risk factors (e.g. obesity) and depression (Chen *et al.,* 2005). These special population characteristics of older Chinese participants aided the assessment of the association of fish consumption with the risk of dementia.

This study has some potential limitations. Firstly, like some previous studies, our four provinces cohort study lack information on the different types (lean, fatty-fish, fresh fish, processed fish, fried fish and seafood) and quantity of fish consumed. This could have affected our inferences on the exact fish types and dementia. But generally, the total fish consumption was inversely associated with the risk of dementia, based on our meta-analysis of cohort studies. Nevertheless, further studies are required to investigate which type of fish consumption has most impact on reduced risk of dementia. Secondly, the self-reported dietary information and the one-off dietary data collected over a two years period could have caused a misclassification of the given information and may not reflect the fish consumption pattern over the whole study follow-up period. Thus, the findings of our Chinese cohort study may be more conservative.

7.6 Conclusion

This chapter study shows that increased consumption of fish is associated with a reduced risk of dementia. This result supports a beneficial effect of increased fish consumption on reducing the risk of dementia, therefore showing the potential importance of consuming fish in preventing dementia worldwide.

Table 7.1: Distribution of socio-demographic and clinical characteristics of participants: Four provinces study, China

Variable	Never eat n (%)	Once a week n (%)	More than twice a week n (%)	Once a day n (%)	P value
Age (years)					
Mean (SD)	69.8 (6.39)	70.8 (7.01)	70.2 (7.02)	70.2 (6.81)	0.041
Sex					
Women	370 (56.6)	433 (54.9)	490 (56.9)	264 (56.7)	0.847
Men	284 (43.4)	356 (45.1)	371 (43.1)	202 (43.3)	
BMI (kg/m^2) §					
Cut-off point					
<20	110 (17.1)	132 (17.2)	159 (19.5)	75 (17.3)	0.157
20-<23	233 (36.2)	262 (34.1)	298 (36.6)	164 (37.9)	
23-<26	198 (30.8)	220 (28.6)	222 (27.3)	105 (24.2)	
>=26	102 (15.9)	154 (20.1)	135 (16.6)	89 (20.6)	
Smoking					
Never-smoking	371 (56.7)	503 (63.8)	583 (67.7)	276 (59.2)	<0.001
Current- or Ex-smoking	283 (43.3)	284 (36.0)	265 (30.8)	187 (40.1)	
unknown	0	2 (0.3)	13 (1.5)	3 (0.6)	
Alcohol drinking in the last 2 years					
Never	493 (75.4)	598 (75.8)	681 (79.1)	321 (68.9)	0.001
Current- or Ex-drinking	159 (24.3)	189 (24.0)	165 (19.2)	132 (28.3)	
Unknown	2 (0.3)	2 (0.3)	15 (1.7)	13 (2.8)	

Urban-rural					
Urban	236 (36.1)	383 (48.5)	384 (44.6)	229 (49.1)	<0.001
Rural	418 (63.9)	406 (51.5)	477 (55.4)	237(50.9)	
Province					
Guangdong	22 (3.4)	107 (13.6)	291 (33.8)	334 (71.7)	<0.001
Shanghai	18 (2.8)	196 (24.8)	516 (59.9)	119 (25.5)	
Heilongjiang	146 (22.3)	220 (27.9)	36 (4.2)	6 (1.3)	
Shanxi	468 (71.6)	266 (33.7)	18 (2.1)	7 (1.5)	
Socio-economic status					
Educational level					
Illiterate	282 (43.1)	320 (40.6)	372 (43.2)	181 (38.8)	<0.001
Primary school	194 (29.7)	244 (30.9)	263 (30.5)	184 (39.5)	
Secondary school	134 (20.5)	118 (15.0)	105 (12.2)	53 (11.4)	
>=High Secondary school	41 (6.3)	72 (9.1)	74 (8.6)	29 (6.2)	
College/University	3 (0.5)	35 (4.4)	44 (5.1)	19 (4.1)	
Unknown	0	0	3 (0.3)	0	
Main occupation					
Peasant	358 (54.7)	379 (48.0)	505 (58.7)	227 (48.7)	<0.001
Manual labourer	95 (14.5)	153 (19.4)	154 (17.9)	95 (20.4)	
Official/Teacher	90 (13.8)	103 (13.1)	71 (8.2)	48 (10.3)	
Business	4 (0.6)	9 (1.1)	13 (1.5)	3 (0.6)	
Housewife	99 (15.1)	85 (10.8)	40 (4.6)	32 (6.9)	
Others	8 (1.2)	60 (7.6)	76 (8.8)	60 (12.9)	
Unknown	0	0	2 (0.2)	1 (0.2)	
Annual income†					
Very satisfactory	48 (7.3)	78 (9.9)	75 (8.7)	52 (11.2)	<0.001

Satisfactory	313 (47.9)	335(42.5)	400 (46.5)	284 (60.9)	
Average	219 (33.5)	298 (37.8)	349 (40.5)	117 (25.1)	
Poor	69 (10.6)	76 (9.6)	35 (4.1)	12 (2.6)	
Unknown	5 (0.8)	2 (0.3)	2 (0.2)	1 (0.2)	
<u>Social network and support</u>					
Marital status					
Married	496 (75.8)	559 (70.8)	684 (79.4)	380 (81.5)	<0.001
Never married/Divorcees	20 (3.1)	18 (2.3)	20 (2.3)	7 (1.5)	
Widowed	138 (21.1)	212 (26.9)	155 (18.0)	79 (17.0)	
Unknown	0	0	2 (0.2)	0	
Living with					
No-one	61 (9.3)	58 (7.4)	58 (6.7)	30 (6.5)	0.202
others	593 (90.7)	731 (92.6)	803 (93.3)	434 (93.5)	
Frequency of visiting children or other relatives					
Never	55 (8.4)	29 (3.7)	33 (3.8)	23 (5.0)	<0.001
Seldom	190 (29.1)	225 (28.5)	229 (26.7)	95 (20.6)	
At least monthly	58 (8.9)	100 (12.7)	106 (12.3)	50 (10.8)	
Once a week	121 (18.5)	167 (21.2)	108 (12.6)	82 (17.7)	
2-3 per week	98 (15.0)	105 (13.3)	68 (7.9)	55 (11.9)	
Everyday	132 (20.2)	163 (20.7)	315 (36.7)	157 (34.0)	
<u>Co-morbidities</u>					
Hypertension (BP ≥140/90 mmHg or taking antihypertensive drugs)					
No	306 (46.8)	386 (48.9)	477 (55.4)	225 (48.3)	0.001
Yes	343 (52.4)	388 (49.2)	354 (41.1)	215 (46.1)	

Unknown	5 (0.8)	15 (1.9)	30 (3.5)	26 (5.6)	
Heart disease					
No	571 (87.3)	657 (83.3)	752 (87.3)	412 (88.4)	0.008
Yes	73 (11.2)	121 (15.3)	96 (11.1)	44 (9.4)	
Unknown ‡	10 (1.5)	11 (1.4)	13 (1.5)	10 (2.1)	
Diabetes					
No	617 (94.3)	747 (94.7)	810 (94.1)	424 (91.0)	0.515
Yes	34 (5.2)	38 (4.8)	46 (5.3)	31 (6.7)	
Unknown ‡	3 (0.5)	4 (0.5)	5 (0.6)	11 (2.4)	
Activity of daily living (score)					
0	609 (93.1)	749 (94.9)	827 (96.1)	448 (96.1)	0.003
1-4	22 (3.4)	29 (3.7)	27 (3.1)	13 (2.8)	
≥5	23 (3.5)	11 (1.4)	7 (0.8)	5 (1.1)	
GMS-AGECAT diagnosis - Depression					
Non-depression	590 (90.2)	733 (92.9)	810 (94.1)	432 (92.7)	0.121
Depression-subcase	26 (4.0)	23 (2.9)	18 (2.1)	16 (3.4)	
Depression-case	38 (5.8)	32 (4.1)	32 (3.7)	17 (3.6)	
Unknown	0	1 (0.1)	1 (0.1)	1 (0.2)	
GMS-AGECAT diagnosis - Dementia					
Non-dementia	546 (83.5)	700 (88.7)	760 (88.3)	383 (82.2)	0.001
Dementia-subcase	56 (8.6)	50 (6.3)	63 (7.3)	51 (10.9)	
Dementia-case	52 (8.0)	38 (4.8)	37 (4.3)	31 (6.7)	
Unknown	0	1 (0.1)	1 (0.1)	1 (0.2)	

Dietary variables

Meat					
Never eat	316 (48.3)	64 (8.1)	11 (1.3)	5 (1.1)	<0.001
Once a week	244 (37.3)	481 (61.0)	108 (12.5)	39 (8.4)	
More than twice a week	69 (10.6)	145 (18.4)	541 (62.8)	51 (10.9)	
Once a day	16 (2.4)	61(7.7)	144 (16.7)	247 (53.0)	
More than twice a day	9 (1.4)	38 (4.8)	57 (6.6)	124 (26.6)	
Egg					
Never eat	82 (12.5)	26 (3.3)	24 (2.8)	20 (4.3)	<0.001
Once a week	82 (12.5)	238 (30.2)	213 (24.8)	142 (30.6)	
More than twice a week	200 (30.6)	214 (27.2)	447 (52.1)	99 (21.3)	
Once a day	270 (41.3)	255 (32.4)	161 (18.8)	151 (32.5)	
More than twice a day	20 (3.1)	55 (7.0)	13 (1.5)	52 (11.2)	
Fresh vegetables					
Never eat	7 (1.1)	5 (0.6)	1 (0.1)	0	<0.001
Once a week	13 (2.0)	18 (2.3)	14 (1.6)	7 (1.5)	
More than twice a week	39 (6.0)	40 (5.1)	45 (5.2)	15 (3.2)	
Once a day	300 (45.9)	324 (41.2)	368 (42.8)	124 (26.7)	
More than twice a day	295 (45.1)	400 (50.8)	432 (50.2)	319 (68.6)	
Fruits					
Never eat	153 (23.4)	72 (9.1)	20 (2.3)	15 (3.2)	<0.001
Once a week	158 (24.2)	200 (25.3)	293 (34.1)	99 (21.4)	
More than twice a week	166 (25.4)	284 (36.0)	227 (26.4)	103 (22.3)	

Once a day	151 (23.1)	182 (23.1)	244 (28.4)	171 (37.0)
More than twice a day	26 (4.0)	51 (6.5)	75 (8.7)	74 (16.0)

*Pearson Chi-Square test, based on data available, not including missing or unknown cases
†Low level of income defined as those having a poor annual income or a serious financial problem in the last 2 years, while high level included those who were not in the low level of income.
‡P-values in the chi-square test are calculated based on available data, not including "Unknown" data.

§Body Mass Index (BMI) (categories cut-off points for overweight and obesity are defined as 23-<26 kg/m^2 and ≥26 kg/m^2, while underweight and normal are <20 kg/m^2 and 20-<23 kg/m^2 respectively) (Ko *et al.*, 2001).

Table 7.2: Numbers of incident dementia and adjusted odd ratios in older people with fish consumption in China

Frequency of fish consumed	Nos of dementia /participants	Person-years	PYAR† (Incidence)	OR[1] 95% CI	OR[2] 95% CI	OR[3] 95% CI	OR[4] 95% CI	OR[5] 95% CI
Never eat	35/654	1967.04	17.79					
Once a week	70/789	2405.88	29.10	Ref*	Ref*	Ref*	Ref*	Ref*
More than twice a week	90/861	2922.98	30.79	0.88 0.59-1.31	0.90 0.60-1.35	0.90 0.60-1.36	1.06 0.65-1.71	1.05 0 .65-1.71
≥once a day	54/466	1396.39	38.67	0.77 0.48-1.23	0.77 0.48- 1.25	0.77 0.47-1.26	0.78 0.44-1.38	0.83 0.47- 1.49
Total	249/2770							

*Reference group taken from "Never eat" and "Once a week"
†PYAR (Incidence): person-year at risk (Incidence rate); Incidence rate per 1000 person-years.
OR[1]: adjusted for age (cont.), sex, province, rural-urban and educational level;
OR[2]: adjusted for age (cont.), sex, province, rural-urban, educational level, BMI, smoking status, and alcohol consumption;
OR[3]: adjusted for age (cont.), sex, province, rural-urban, educational level, BMI, smoking status, alcohol consumption, marital status, frequency of visiting children or other relatives, hypertension (yes or no), diabetes, heart disease, stroke, activity of daily living and depression
OR[4]: in OR[3] model, plus adjustment for meat consumption and egg
OR[5]: in OR[4] model, plus adjustment for vegetable and fruit

Table 7.3: Numbers of incident dementia and adjusted odd ratios among men and women older adults with fish consumption in China

	Women				Men			
Frequency of fish consumed	Nos of dementia /participants	Person-years	PYAR† (Incidence)	OR^5 95% CI	Nos of dementia /participants	Person-years	PYAR† (Incidence)	OR^5 95% CI
"Never eat" or "Once aweek"	73/803	2429.05	30.05	Ref*	32/640	1943.86	16.46	Ref*
More than twice a week	70/490	1655.14	42.29	1.23 0.69-2.19	20/371	1267.84	15.77	0.67 0.23-1.90
≥once a day	42/264	792.67	52.99	1.000 0.50-2.00	12/202	603.72	19.88	0.55 0.17-1.81
Total	185/1557				64/1213			

*Reference group taken from "Never eat" and "Once a week"
†PYAR (Incidence): person-year at risk (Incidence rate); Incidence rate per 1000 person-years.
OR^5: the same as that in Table 2 above

CHAPTER EIGHT: IMPACT OF FISH CONSUMPTION IN OLDER AGE ON ALL-CAUSE MORTALITY: THE FIVE-PROVINCE COHORT STUDY

8.1 Introduction

Fish is a nutritional source of high-quality animal protein and various essential nutrients, including vitamins, minerals and amino acids (Kawarazuka, 2010; Lund, 2013; FAO, 2018). It is the major source of long-chain omega-3 polyunsaturated fatty acids (PUFAs) with various protective health properties (Wallin *et al.*, 2012; Lund, 2013). Regardless of its beneficial role on some major chronic diseases e.g. cardiovascular disease (CVD) (Bonaccio *et al.*, 2017) and neurodegenerative disorders (Zhang *et al.*, 2016), findings from epidemiological studies of association between fish consumption and the risk of all-cause mortality are inconsistent. Some studies suggested an association of fish consumption with reduced all-cause mortality (Takata *et al.*, 2013; Zhang *et al.*, 2018), while others showed no association (Osler, Andreasen, Hoidrup, 2003; Engeset *et al.*, 2015). Likewise, studies have shown the association between fish consumption with cause specific mortality including total CVD (Yamagishi *et al.*, 2008) ischemic stroke and diabetes (Takata *et al.*, 2013), while studies that specifically assessed the association of fish consumption and dementia specific mortality are rare. Also, few studies have assessed the association of fish consumption with all-cause mortality among the Chinese population. Therefore, this study was conducted to investigate the impact of fish consumption on all-cause mortality in older people and examine differences in the impact between people with and without dementia using a Chinese population-based cohort data.

8.2 Methods

8.2.1 Multi-province health survey study of older people in China

The study population was derived from the multi-province health survey study in China. The methods of the study, populations and interview have been fully described elsewhere (Chen *et al.,* 2013; Chen *et al.,* 2014) and in Chapter 3 the methodology section above (3.6.1.6). In 2007-2009, data was collected among older people in the provinces of Anhui, Guangdong, Heilongjiang, Shanghai and Shanxi in China to investigate the prevalence, risk factors and dementia care and other chronic conditions (Chen *et al.,* 2012; Chen *et al.,* 2013).

8.2.1.1 The Four-province study

In 2008-2009, we selected one rural and one urban community from each of the four provinces (Guangdong, Heilongjiang, Shanghai, Shanxi) as the study fields. We tried to recruit no fewer than 500 participants in each community and employed a cluster randomised sampling method to choose residential communities (the district in urban areas and the village in rural) from each of the four provinces. The target population consisted of residents aged ≥60 years living in the area for at least 5 years. Based on the residency list of the committees of the village and the district, we recruited a total of 4314 participants with an overall response rate of 93.8%. The local survey team interviewed the participants at home. The main interview included a general health and risk factors record, the Geriatric Mental State (GMS) questionnaire (Copeland *et al.,* 2002) and other components of the 10/66 algorithm dementia research package (Prince *et al.,* 2003). We carried out a two-phase interview to save our research resources. In phase one, we completed the general health and risk factors record, the GMS, the Community Screening Instrument for Dementia (CSI-D) cognitive test and Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Using three of the four constituent components of the 10/66 algorithm (i.e. data of GMS-AGECAT, the CSI-D cognitive test and CERAD interview), we calculated a probability of possible dementia for each participant. In phase two, we selected the top 15% of the population who had the highest probability of having “dementia” as “probable cases” and a random sample of 5% of the rest as “probable non-cases” for subsequent interviews in each province. The interview team completed the CSI-D informant interview for the selected participants. In 2011-2012, a followed-up data was collected from a total of 2892 surviving cohort members using the same interview materials and 259 deaths were recorded.

8.2.1.2 The Anhui Study

At baseline, 1810 participants aged ≥65years old who had lived for more than five years in the Yiming subdistrict of Hefei city were randomly recruited in 2001 (Chen *et al.,* 2004; Chen *et al.*, 2012). An additional 1709 participants aged 60 years and above were further recruited in 2003, from all the 16 villages in Tangdian district of Yingshang county (Chen *et al.,* 2005). A total of 3336 older participants (response rate of 94.8%), of whom 1736 were from urban and 1600 from the rural area completed the interview conducted by trained survey team from the Anhui Medical University. Using the same method of interview, 2806 surviving participants were re-interviewed one year after the baseline examination (Wave 2) (Chen *et al.*, 2008). Six years after the baseline interview, we successfully re-interviewed 1757 survivors in the year 2007 and 2009 (Wave 3) (Chen *et al.,* 2014). In 2011-2012, a followed-up data was collected from a total of 944 surviving cohort members using the same interview materials and 70 deaths were recorded. All the participants that agreed to be interviewed signed a written informed consent, and the nearest relative or caregiver of those participants (approximately 5%) that were unable to consent were approached for permission to participate. Socio-demographic characteristics of each participants including their occupational class, level of income, educational attainment, urban-rurality, social networks and support, lifestyle, histories of chronic diseases and risk factors were documented using the general health and risk factor record and the Geriatric Mental State (GMS) questionnaire respectively (Wave 1) (Chen *et al.*, 2004; Chen *et al.*, 2005). The anthropometric data and blood pressure of each participant was measured, while their dementia and depression status were diagnosed using the Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy (GMS-AGECAT) data (Chen *et al.*, 2004). Participants' dietary intake details including the intake of rice, wheat flour, meat, fish, egg, fresh vegetable, fruit, chilli pepper, garlic, ginger and different types of vegetable oils were documented. Participants fish consumption frequency in the past two years were documented as (1) Never eat, (2) ≤Once a week, (3) >Once a week and < Daily, (4) Once a day, and (5) ≥ Twice a day.

8.2.2 Death Ascertainment

The local residential areas were visited to obtain information about participants' survival status through resident committees, family members, neighbours and friends. The electronic registration databases from the Centre for Disease Control and Police Registration were reviewed to identify mortality and causes of deaths in the urban cohort. A standard verbal autopsy questionnaire was employed to further identify other causes of death from family members, relatives, neighbours or friends of the deceased.

8.3 Data Analysis

We examined the distributions of the socio-demographic and clinical characteristics of participants with all-cause mortality using chi-squared test for categorical variables and one-way analysis of variance for continuous outcome variables. The person-years at risk for each of the participants were computed from the beginning of the cohort. The mortality rate per 1000 person-years was also computed for each level of fish consumption. A cox proportional hazards regression model was employed to assess the association of any levels of fish consumption over the past two years versus those that “never eat” and all-cause mortality using the follow-up person-years as the time metric. We computed the hazard ratios (HR) and 95% confidence intervals of each fish consumption level associated with all-cause mortality over a follow up period of 3-years. Seven models were employed to adjust for different co-variables that might confound or mediate the association of fish consumption and all-cause mortality. In model 1, we computed the unadjusted HR for different levels of fish consumption in relation to all-cause mortality using the lowest fish consumption level (never eat) as the reference category. We further adjusted for age (cont.) and sex in the second model. In model 3, further adjustment was made for body mass index (BMI), smoking status and alcohol consumption. In model 4, we additionally adjusted for province, urban-rural, educational level, occupational class, and income plus all the variables in model 3. Apart from all the previous variables, adjustment was made for marital status and frequency of visiting children or other relatives in the fifth model. In addition to all the previous variables, further adjustment was made for hypertension, heart disease, diabetes, activity of daily living, depression and cognitive impairment/dementia in the sixth model. In the final model, additional adjustment was made, which included all variables in the previous model plus the dietary intakes variables that include meat, fish, egg, vegetable, and fruit. To increase the statistical power of the association and the level of significant the last two fish consumption levels (once a day and more than twice a day) were combined due to small sample sizes and all the multivariate adjusted analysis was repeated for all the previous models. Finally, to further increase the significant level of the association, the last three fish consumption levels (More than twice a week, once a day and more than twice a day) were combined and the HR computed following the same multivariate adjusted analysis models. All data analyses were conducted using SPSS version 20 software (SPSS Inc., Chicago, IL). P values <0.05 were considered statistically significant.

8.4 Results

8.4.1 The five-provinces study in China

Of 4165 participants, 3836 surviving cohort members were interviewed and 329 deaths from all causes (including 61 dementia deaths cases) were documented during a 3 years follow-up period (12358.25 person-years). The participants' average age (SD) was 72.1 (7.32) years and 55.3% were women. A total of 988 (23.9%) participants "never" consumed fish over the past two years, 1327 (32.1%) consumed fish "once a week", 1209 (29.3%) consumed fish "more than twice a week", and 607 (14.7%) consumed fish ≥once a day. Table 1 shows the numbers and percentages of the socio-demographic and clinical characteristics of both death and alive study participants.

8.4.2 Fish consumption and all-cause mortality

Table 2 shows the total person-years, mortality rate per 1000 person-years, univariate, age-sex adjusted and multivariate adjusted HRs and 95% CIs of all-cause mortality in different levels of fish consumption compared with "never eat". The unadjusted HR showed a significant reduction in the risk of all-cause mortality when the highest fish consumption level (≥once a day) was compared with the lowest fish consumption level (never eat). Similarly, the age-sex adjusted analysis model showed a significant reduction in the risk of all-cause mortality when the moderate (Once a week) and the highest fish consumption levels were compared with the lowest fish consumption level.

In the multivariate adjusted analysis models, similar significant reduction in the risk of all-cause mortality was observed with gradual decrease in hazard ratio up until the 4th model, when the highest fish consumption level was compared with the lowest fish consumption level. The significant levels were maintained in the 5th and the 6th models with slight increase in hazard ratios. The fully adjusted model 7 showed a 41% significant reduction in the risk of all-cause mortality (HR 0.59, 95% CI 0.35-0.99) among the participants that consumed fish "≥ once a day" when compared with those that "never eat".

8.4.3 Fish consumption and mortality in people with dementia

Table 3 shows the total person-years, mortality rate per 1000 person-years, univariate, age-sex and the multivariate adjusted HRs of mortality and 95% CIs of different levels of fish consumption compared with "never eat" in people with dementia. The age-sex adjusted analysis model showed a non-significant positive association of fish consumption with the risk of mortality.

In the multivariate adjusted analysis models, increased mortality was observed among moderate fish consumers of "Once a week" when compared with "never eat", but not statistically significant. Conversely, no significant increase of mortality was observed across all levels of fish consumption in people with dementia, with hazard ratios close to or crossing 1.0 and all the confidence intervals crossing 1.0, when the highest fish consumption level "≥ once a day" was compared with the lowest fish consumption level "never eat" irrespective of the kind of models used. The fully adjusted model 7 showed a 31% increased risk of mortality in people with dementia (HR 1.31, 95% CI 0.27-6.46) when the highest fish consumption level "≥ Once a day" was compared with the lowest fish consumption level "never eat", but it was not statistically significant. There was no significant association of moderate fish consumption with mortality (HR 1.06, 95% CI 0.30-3.71).

Hence, the result presented appears to show no association of increased consumption of fish with all-cause mortality in people with dementia.

8.4.4 Fish consumption and mortality in people without dementia

Table 4 shows the total person-years, mortality rate per 1000 person-years, univariate, age-sex and the multivariate adjusted HRs of mortality and 95% CIs of different levels of fish consumption compared with "never eat" in people without dementia. The unadjusted HR showed a significant reduction in the risk of mortality when the highest fish consumption level (≥once a day) was compared with the lowest fish consumption level (never eat). Similarly, the age-sex adjusted analysis model showed a significant reduction in the risk of mortality when the moderate (Once a week) and the highest fish consumption levels was compared with the lowest fish consumption level.

In the multivariate adjusted analysis models, similar significant reduction in the risk of mortality was observed with gradual increase in hazard ratio up until the 6^{th} model, when the highest fish consumption level was compared with the lowest fish consumption level, while the moderate fish consumption level showed a non-significant reduction in the risk of mortality across the 4^{th}, 5^{th}, 6^{th} and the 7^{th} models with slight increase in hazard ratios. The fully adjusted model 7 showed a 41% marginal significant reduction in the risk of mortality (HR 0.59, 95% CI 0.34-1.03) among the participants that consumed fish "≥ once a day" when compared with those that "never eat".

8.5 Discussion

This Chapter population-based cohort study revealed a significant inverse association between fish consumption and all-cause mortality in older Chinese. It was from older people without dementia, but not from those with dementia, suggesting no beneficial effect for increased consumption of fish on survival in people who had dementia.

8.5.1 Fish consumption and all-cause mortality

The inverse association of fish consumption with all-cause mortality found in this study is consistent with the findings of some previous studies. A longitudinal cohort study of 8825 white and black male and female participants aged 25-74 years found reduced risk of all-cause mortality when the highest fish consumption "> once/week" was compared with never eat (Gillum, Mussolino and Madans, 2000). Similarly, a Hongkong Chinese case-control study of 36,003 participants with mean age of 70.2 and 71.2 years for cases and control respectively revealed a significant reduction in the risk of all-cause mortality when the highest fish consumption level of ≥4 times/week was compared with lowest fish consumption level of ≤3 times/month (OR 0.80, 95% CI 0.68-0.94) (Wang *et al.,* 2011). This resonates with a US National Institutes of Health (NIH)-AARP diet and Health cohort study of 421 309 participants aged 50-71 years with 85 112 deaths and a follow up period of 16 years that found a significant reduction in the risk of total mortality, when the highest quintile of fish consumption was compared with the lowest quintile (Zhang *et al.,* 2018). A Shanghai Chinese cohort study of 18 244 participants also found a significant reduction in the risk of all-cause mortality when the highest fish consumption level (≥200 g/week) was compared with the lowest fish consumption level (<50g/week) (Yuan *et al.*, 2001). Equally, in a US Vitamins and Lifestyle cohort Study (VITAL Study) of 70 495 participants aged 50-76 years with 3051 death and a follow up period of 5 years, Bell *et al.* (2014) found a significant reduction in the risk of all-cause mortality when the highest fish consumption was compared with the lowest fish consumption. Another Chinese prospective cohort study of 134 296 participants aged 40-74 years and 5836 total deaths found a reduced risk of all-cause mortality (HR 0.84, 0.76-0.92), when the highest quintile of fish consumption was compared with the lowest quintile of fish consumption (Takata *et al.*, 2013). Correspondingly, an inverse association of total fish consumption with all-cause mortality was found among all participants in a US Southern Community Cohort Study (SCCS) of 77,604 participants aged 40-79 years and 6,914 deaths with 5.5 years follow-up period, when highest quintile of fish consumption was compared with the lowest quintile (RR 0.92, 0.84-1.00) (Villegas *et al.*, 2015).

However, no association of all-cause mortality was observed when higher fish consumption was compared with moderate fish consumption in two European studies (Osler, Andreasen, Hoidrup, 2003; Engeset *et al.*, 2015), but Engeset *et al.* (2015) found a U shape trend in the risk of all-cause mortality and fatty fish consumption. Nakamura *et al.* (2005) Japanese cohort study of 8,879 participants aged ≥30 years with 19 years follow up period also observed (RR 0.99, 0.77-1.27) for all-cause mortality, when the highest fish consumption ≥2 times/day was compared with the lowest fish consumption 1-2 times/week. The discrepancies in the results could be from sampling variation and could be attributed to the cohort characteristics including an increased number of people with dementia but the studies did not stratify data for analysis. The discrepancies could also be attributed to the different cooking techniques in countries, since fish is popularly deep-fried in the Western regions while grilling and steaming are popular with the Asians. This deep-frying could negatively impact on the protective effects of the constituents in fish through trans-fatty acids production and inflammation induction, which are two major causes of chronic diseases. Likewise, the various types of fish consumed in countries do have different biological and nutritional composition, which could have affected the impact of the association.

The inverse association between fish consumption and all-cause mortality observed in this study (but not in the population of people with dementia) and other studies is biologically plausible, because of the readily available omega-3 PUFA constituents in fish (Uauy and Dangour, 2006; Connor and Connor, 2007). The protective effect of fish consumption and its omega-3 PUFA constituents on chronic diseases have been demonstrated in previous studies (Zheng *et al.*, 2012; Xun and He, 2012) through the impact of their anti-inflammatory (Calder, 2013), anti-atherosclerotic, antithrombotic (Chapkin *et al.*, 2007), antiarrhythmic and antiatherogenic properties (Thorgilsson, Nunes and Gunnlaugsdóttir, 2010; Mori, 2017).

8.5.2 Fish consumption and mortality in people with dementia

This Chapter study found that higher fish consumption was associated with increased risk of mortality in people with dementia, which was not statistically significant. In contrast, a recent US prospective cohort study of 421,309 participants aged 50-71 years and 85,112 total deaths with 16 years follow up period found a significant inverse association between fish consumption and Alzheimer's disease mortality (Zhang *et al.*, 2018). The differences between the Chinese study and the US study (Zhang *et al.*, 2018) could be due to differences in the sample size and duration of the follow-up. Also, it could be due to the type of dementia assessed and different ethnicity. Further studies are required to elucidate the association of fish consumption with mortality in people with dementia.

8.5.3 Fish consumption and mortality in people without dementia

This Chapter study found that increased fish consumption was associated with reduced risk of mortality in people without dementia, which was different from the findings in older people with dementia. The differences between the two findings in this study could be attributed to the characteristics of older people with and without dementia. There could be a reverse association between fish consumption and dementia in older people with dementia due to a short-term follow up of the cohort.

8.5.4 Strengths and Limitations of the study

The main strength of this study is its prospective cohort design, and detailed confounding variables available that allowed us to comprehensively explore their roles in the association of fish consumption with all-cause mortality in people with and without dementia.

This Chapter study has some limitations. Firstly, like some other previous studies, our 5-province study lack information on the different types (lean, fatty-fish, fresh fish, processed fish, fried fish and seafood) and quantity of fish consumed. This could have affected our inferences on the exact fish types associated with all-cause mortality. But generally, total fish consumption was significantly and inversely associated with the risk of all-cause mortality. Although there are previous studies conducted on specific types of fish in relation to all-cause mortality, further studies are still required to ensure proper public health recommendations are made to the populace. Secondly, the self-reported dietary information and the one-off dietary data collection over a two years period could have caused a misclassification of the given information and may not reflect the fish consumption pattern over the whole study follow-up period.

8.6 Conclusion

This Chapter demonstrated an inverse association of fish consumption at older age and all-cause mortality, which was in the population free from dementia but not in people with dementia. Increased consumption of fish in older people significantly reduced all-cause mortality. However, it could not help to prolong life in people with dementia. It should be better to increase consumption of fish in the general population to prevent dementia, then increasing the life expectancy in the world. Further cohort studies are required to elucidate the association of fish consumption with mortality in people with dementia.

Table 8.1: Distribution of socio-demographic and clinical characteristics of participants: five province study, China

Variable	All Participants N=4165		Death n=329	(%)	Alive n=3836	(%)	P value
Age (years)							
Mean (SD)	72.1	7.32	76.7	7.64	71.7	7.16	*<0.001*
Sex (n, %)							
Women	2304	55.3	150	45.6	2154	56.2	*<0.001*
Men	1861	44.7	179	54.4	1682	43.8	
BMI (kg/m^2) §							
Cut-off point							
<20	816	19.6	97	29.5	719	18.7	*<0.001*
20-<23	1428	34.3	112	34.0	1316	34.3	
23-<26	1063	25.5	62	18.8	1001	26.1	
>=26	651	15.6	37	11.2	614	16.0	
unknown	207	5.0	21	6.4	186	4.8	
Smoking							
Never-smoking	2576	61.8	182	55.3	2394	62.4	*0.010*
Current- or Ex-smoking	1537	36.9	143	43.5	1394	36.3	
unknown	52	1.2	4	1.2	48	1.3	
Alcohol drinking in the last 2 years							
Never	3045	73.1	228	69.3	2817	73.4	*0.130*

Current- or Ex-drinking	1051	25.2	94	28.6	957	24.9	
Unknown	69	1.7	7	2.1	62	1.6	
Urban-rural							
Urban	1730	41.5	135	41.0	1595	41.6	*0.847*
Rural	2435	58.5	194	59.0	2241	58.4	
Province							
Guangdong	902	21.7	74	22.5	828	21.6	*0.340*
Shanghai	926	22.2	71	21.6	855	22.3	
Heilongjiang	460	11.0	33	10.0	427	11.1	
Shanxi	863	20.7	81	24.6	782	20.4	
Anhui	1014	24.3	70	21.3	944	24.6	
Socio-economic status							
Educational level							
Illiterate	1984	47.6	198	60.2	1786	46.6	*<0.001*
Primary school	1100	26.4	69	21.0	1031	26.9	
Secondary school	548	13.2	27	8.2	521	13.6	
>=High Secondary school	325	7.8	23	7.0	302	7.9	
College/University	175	4.2	10	3.0	165	4.3	
Unknown	33	0.8	2	0.6	31	0.8	
Main occupation							
Peasant	2321	55.7	195	59.3	2126	55.4	*0.384*
Manual labourer	628	15.1	42	12.8	586	15.3	
Official/Teacher	536	12.9	39	11.9	497	13.0	
Business	32	0.8	1	0.3	31	0.8	
Housewife	338	8.1	32	9.7	306	8.0	

Others	278	6.7	18	5.5	260	6.8	
Unknown	32	0.8	2	0.6	30	0.8	
Annual income†							
Very satisfactory	333	8.0	23	7.0	310	8.1	*0.013*
Satisfactory	1828	43.9	124	37.7	1704	44.4	
Average	1653	39.7	142	43.2	1511	39.4	
Poor	308	7.4	36	10.9	272	7.1	
Unknown	43	1.0	4	1.2	39	1.0	
Social network and support							
Marital status							
Married	3026	72.7	194	59.0	2832	73.8	*<0.001*
Never married/Divorcees	112	2.7	9	2.7	103	2.7	
Widowed	997	23.9	125	38.0	872	22.7	
Unknown	30	0.7	1	0.3	29	0.8	
Living with							
No-one	425	10.3	50	15.4	375	9.9	*0.002*
others	3705	89.7	275	84.6	3430	90.1	
Frequency of visiting children or other relatives							
Never	234	5.7	37	11.4	197	5.2	*<0.001*
Seldom	1050	25.5	72	22.2	978	25.8	
At least monthly	435	10.6	29	9.0	406	10.7	
Once a week	650	15.8	38	11.7	612	16.1	

2-3 per week	619	15.0	52	16.0	567	14.9	
Everyday	1134	27.5	96	29.6	1038	27.3	
Co-morbidities							
Hypertension (BP ≥140/90 mmHg or taking antihypertensive drugs)							
No	2128	51.1	145	44.1	1983	51.7	*0.009*
Yes	1882	45.2	170	51.7	1712	44.6	
Unknown	155	3.7	14	4.3	141	3.7	
Heart disease							
No	3524	84.6	279	84.8	3245	84.6	*0.897*
Yes	545	13.1	40	12.2	505	13.2	
Unknown ‡	96	2.3	10	3.0	86	2.2	
Diabetes							
No	3878	93.1	303	92.1	3575	93.2	*0.601*
Yes	228	5.5	20	6.1	208	5.4	
Unknown ‡	59	1.4	6	1.8	53	1.4	
Activity of daily living (score)							
0	3713	89.1	241	73.3	3472	90.5	*<0.001*
1-4	295	7.1	38	11.6	257	6.7	
≥5	157	3.8	50	15.2	107	2.8	
GMS-AGECAT diagnosis - Depression							

Non-depression	3831	92.0	297	90.3	3534	92.1	*0.435*
Depression-subcase	126	3.0	10	3.0	116	3.0	
Depression-case	183	4.4	19	5.8	164	4.3	
Unknown	25	0.6	3	0.9	22	0.6	
GMS-AGECAT diagnosis -Dementia							
Non-dementia	3317	79.6	227	69.0	3090	80.6	*<0.001*
Dementia-subcase	417	10.0	38	11.6	379	9.9	
Dementia-case	406	9.7	61	18.5	345	9.0	
Unknown	25	0.6	3	0.9	22	0.6	
Dietary variables							
Fish							
Never eat	988	23.9	98	30.2	890	23.4	*0.014*
Once a week	1327	32.1	110	33.8	1217	32.0	
More than twice a week	1209	29.3	77	23.7	1132	29.7	
Once a day	446	10.8	26	8.0	420	11.0	
More than twice a day	161	3.9	14	4.3	147	3.9	
Meat							
Never eat	710	17.2	70	21.5	640	16.8	*0.222*
Once a week	1387	33.6	110	33.8	1277	33.6	
More than twice a week	1129	27.3	78	24.0	1051	27.6	
Once a day	631	15.3	48	14.8	583	15.3	
More than twice a day	274	6.6	19	5.8	255	6.7	
Egg							
Never eat	272	6.6	29	9.0	243	6.4	*0.222*
Once a week	981	23.8	86	26.5	895	23.6	

More than twice a week	1418	34.4	101	31.2	1317	34.7	
Once a day	1272	34.4	93	28.7	1179	31.0	
More than twice a day	181	4.4	15	4.6	166	4.4	
Fresh vegetables							
Never eat	20	0.5	1	0.3	19	0.5	*0.360*
Once a week	86	2.1	11	3.4	75	2.0	
More than twice a week	207	5.0	18	5.6	189	5.0	
Once a day	1685	40.8	122	37.7	1563	41.1	
More than twice a day	2127	51.6	172	53.1	1955	51.4	
Fruits							
Never eat	485	11.8	50	15.4	435	11.5	*0.113*
Once a week	1268	30.8	105	32.4	1163	30.6	
More than twice a week	1105	26.8	75	23.1	1030	27.1	
Once a day	969	23.5	68	21.0	901	23.7	
More than twice a day	292	7.1	26	8.0	266	7.0	

*Pearson Chi-Square test, based on data available, not including missing or unknown cases
†Low level of income defined as those having a poor annual income or a serious financial problem in the last 2 years, while high level included those who were not in the low level of income.
‡P-values in the chi-square test are calculated based on available data, not including “Unknown” data.

§Body Mass Index (BMI) (categories cut-off points for overweight and obesity are defined as 23-<26 kg/m^2 and ≥26 kg/m^2, while underweight and normal are <20 kg/m^{2}and 20-<23 kg/m^2 respectively) (Ko *et al.*, 2001).

Table 8.2: Numbers of death and adjusted hazard ratios of mortality in older people with different level of fish consumption

Fish consumption	Nos. of incident death/participants	Person-years	Mortality rate*	HR[1]† 95% CI	HR[2] 95% CI	HR[3] 95% CI	HR[4] 95% CI	HR[5] 95% CI	HR[6] 95% CI	HR[7] 95% CI
Never eat	98/988	2848.52	34.40	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Once a week	110/1327	3875.83	28.38	0.82 0.63-1.08	0.70 0.53-0.93	0.71 0.53-0.95	0.69 0.50-0.96	0.74 0.53-1.04	0.78 0.56-1.10	0.79 0.53-1.18
≥ Once a day	117/1816	5633.90	20.77	0.59 0.45-0.78	0.56 0.42-0.74	0.54 0.40-0.72	0.55 0.36-0.84	0.59 0.38-0.91	0.61 0.39-0.95	0.59 0.35-0.99
Total	325/4131									

* Mortality rate per 1000 person-years.
HR[1]: unadjusted for;
HR[2]: adjusted for age (cont.), sex,
HR[3]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption;
HR[4]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income
HR[5]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives;
HR[6]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives, hypertension, heart disease, diabetes, activity of daily living, depression and cognitive impairment/dementia;
HR[7]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives, hypertension, heart disease, diabetes, activity of daily living, depression and cognitive impairment/dementia, + dietary intake: eg, meat, fish, egg, vegetables, fruits

Table 8.3: Number of death and adjusted hazard ratios in older people with dementia in China

Fish consumption	Nos. of incident death/participants	Person-years	Mortality rate*	HR[1]† 95% CI	HR[2] 95% CI	HR[3] 95% CI	HR[4] 95% CI	HR[5] 95% CI	HR[6] 95% CI	HR[7] 95% CI
Never eat	17/123	327.50	51.91	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Once a week	20/139	388.04	51.54	1.00 0.52-1.90	0.94 0.41-2.15	0.90 0.37-2.18	0.93 0.36-2.42	0.94 0.34-2.55	0.95 0.35-2.63	1.06 0.30-3.71
≥once a day	24/143	387.79	61.89	1.18 0.63-2.21	0.97 0.45-2.09	0.97 0.41-2.32	1.04 0.30-3.56	1.05 0.30-3.70	1.09 0.30-3.97	1.31 0.27-6.46
Total	61/405									

*Mortality rate per 1000 person-years.
HR[1]: unadjusted for;
HR[2]: adjusted for age (cont.), sex,
HR[3]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption;
HR[4]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income
HR[5]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives;
HR[6]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives, hypertension, heart disease, diabetes, activity of daily living, depression and cognitive impairment/dementia;
HR[7]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives, hypertension, heart disease, diabetes, activity of daily living, depression and cognitive impairment/dementia, + dietary intake: eg, meat, fish, egg, vegetable, fruit.

Table 8.4: Numbers of death and adjusted hazard ratios in older people without dementia in China

Fish consumption	Nos. of incident death/participants	Person-years	Mortality rate*	HR1† 95% CI	HR2 95% CI	HR3 95% CI	HR4 95% CI	HR5 95% CI	HR6 95% CI	HR7 95% CI
Never eat	69/ 746	2176.79	31.70	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Once a week	74/1046	3096.59	23.90	0.75 0.54-1.04	0.67 0.48- 0.93	0.70 0.50- 0.97	0.74 0.51-1.07	0.77 0.53-1.13	0.84 0.57-1.24	0.84 0.54-1.30
≥once a day	81/1512	4774.71	16.96	0.52 0.38-0.72	0.49 0.36-0.68	0.51 0.37- 0.71	0.51 0.32- 0.82	0.55 0.34-0.88	0.58 0.36-0.94	0.59 0.34-1.03
Total	224/ 3304									

*Mortality rate per 1000 person-years.
HR[1]: unadjusted for;
HR[2]: adjusted for age (cont.), sex,
HR[3]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption;
HR[4]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income
HR[5]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives;
HR[6]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives, hypertension, heart disease, diabetes, activity of daily living, depression and cognitive impairment/dementia;
HR[7]: adjusted for age (cont.), sex, BMI, smoking status, alcohol consumption, province, urban-rural, educational level, occupational class, income, marital status, frequency of visiting children or other relatives, hypertension, heart disease, diabetes, activity of daily living, depression and cognitive impairment/dementia, + dietary intake: eg, meat, fish, egg, vegetable, fruit

CHAPTER NINE: IMPACT OF FISH CONSUMPTION ON DEMENTIA AND OTHER HEALTH OUTCOMES: FOCUS GROUP RESEARCH

9.1 Introduction

Previous studies suggested that increased consumption of fish reduces the risk of cardiovascular diseases and improve the outcomes (Raatz *et al.,* 2013). However, it is unclear whether these impacts remain among people with dementia. Despite fish being associated with low morbidities and mortality in all populations due to its long chain omega-3 polyunsaturated fatty acids constituent and other essential nutrients, its habitual consumption and its determinants in older people have not been well investigated. Previous studies investigating the association between fish consumption and dementia and the determinants of fish consumption in older age are predominantly of quantitative design (Barberger-Gateau *et al.,* 2007; Devore *et al.,* 2009; Lopez *et al.,* 2011). However, the quantitative studies could not reflect people's experience and views on the association and the determinants of fish consumption in older age. It is expected that through discussing with older people, we will better understand older people's views on dementia and other health outcomes in relation to fish consumption and the determinants that affect their consumption of fish. Therefore, as part of my doctoral research, this study aimed to explore the views and perception of older people on the association of fish consumption with the risk of dementia and the determining factors that can affect the consumption of fish using a qualitative design approach. This chapter study aimed to complement the quantitative findings of this research.

9.2 Methods

Focus group discussion, a qualitative design approach was employed in this part of the study. The methods of the study have been fully described in Chapter 3 the methodology section (3.6.3) above.

In brief, using a convenient non-probability sampling approach, older adults aged 60 and above who resided in the Wolverhampton area of the West Midlands, UK, were invited through a local religious organisation to participate in this study. Out of 18 adults who showed an expression of interest to take part, 12 adults agreed and consented to participate in the two discussions. A semi-structured discussion guide was developed and used to collect the required information. The participants were asked to sign written informed consent. The two focus group discussions lasted for approximately 60 minutes each and took place three weeks apart.

9.3 Data analysis

The audio recorded focus group discussions were uploaded onto the computer and transcribed verbatim in Microsoft Word. The Nvivo version 11 qualitative software program was used to organise, store and manage the data during transcription before manually embarking on thematic analysis. The transcribed discussions were analysed using the six thematic analysis steps of Braun and Clarke (2006). These six phases that include familiarisation with the data, initial codes generation, searching for themes, reviewing themes, defining and naming themes, and producing the analysis report are all outlined in the methodology chapter 3 section (3.6.3.4.5) above. All the themes that emerged were checked and compared with the transcript to ensure reliability and any doubts or differences were resolved through discussion (Strudwick and Morris, 2010). A thematic map was created for the two discussions that drew on all the main themes from the participants.

9.4 Results

9.4.1 Demographic Characteristics

A total of 12 participants participated in the two focus group discussions of whom eight were males and four were females. Majority of the participants were from the White British ethnic background

(83.3%), while the rest of the participants were from the Black British ethnic background. Their mean age was 67.6 years (SD ±10.3). Table 9.1 shows the participants demographic characteristics.

Table 9.1: Demographic Characteristics of Participants for the Focus Group Study

Demographic Characteristics	N (%) of Participants
Age (yrs) [Mean ± SD]	67.6 (±10.3)
Sex	
Males	8 (66.7)
Female	4 (33.3)
Marital status	
Married	6 (50.0)
Never married	1 (8.3)
Widow	5 (41.7)
Income	
800-1000	4 (33.3)
1000-3000	6 (50.0)
>3000	2 (16.7)
Occupational class	
Public sector	2 (16.7)
Private sector	1 (8.3)
Self employed	1 (8.3)
Retired	8 (66.7)
Educational background	
Secondary school	3 (25.0)
University degree	3 (25.0)
Graduate	3 (25.0)
Other	3 (25.0)
Ethnicity	
White British	10 (83.3)
Black British	2 (16.7)

9.4.2 *Findings from Thematic Analysis*

The findings presented were based on the summary of the thematic analysis from the two focus group discussions. The themes had several subthemes within them. There were some similarities among the initial codes which graduated into subthemes and then into the overarching theme that summarises the whole discussion. The similar subthemes arising from the focus group discussions were grouped together under main subtheme headings. First, the over-arching themes that emerged from the discussions were mentioned, followed by a combined thematic map showing each over-arching theme and their subthemes together and finally the presentation of the findings from the overarching themes using extract from the transcripts. Following the data collection, transcription and analysis stage, five significant over-arching themes emanated from the two focus group discussions. These include:

1. Fish consumption habits
2. Perceived enablers/barriers of fish consumption
3. Perceived benefit of eating fish
4. Commonly consumed fish
5. Participant’s concern

The thematic analysis process generated significant concepts evolving from the data. These important themes provided some plausible understanding to the findings from the quantitative phase of the study. These findings showed the common and similar responses from all the participants. Each over-arching theme consists of subthemes that are illustrated using thematic maps. These will be sequentially discussed and explored using extracts from the transcript to buttress the points made by the research participants during the discussion. These extracts were applied according to their suitability to the themes being discussed. Outlined below are the themes and subthemes.

9.4.2.1 *Theme 1. Fish consumption habits*

One of the themes that emerged from the focus group discussions is the theme “Fish consumption habits”. Majority of the participants have developed their fish consumption habit over the years. This analysis phase reflects the participants fish consumption habits. This will be discussed under three subthemes including:

A. Occasional fish consumption
B. Number of times fish is consumed per week/month

C. Days of the week fish is consumed

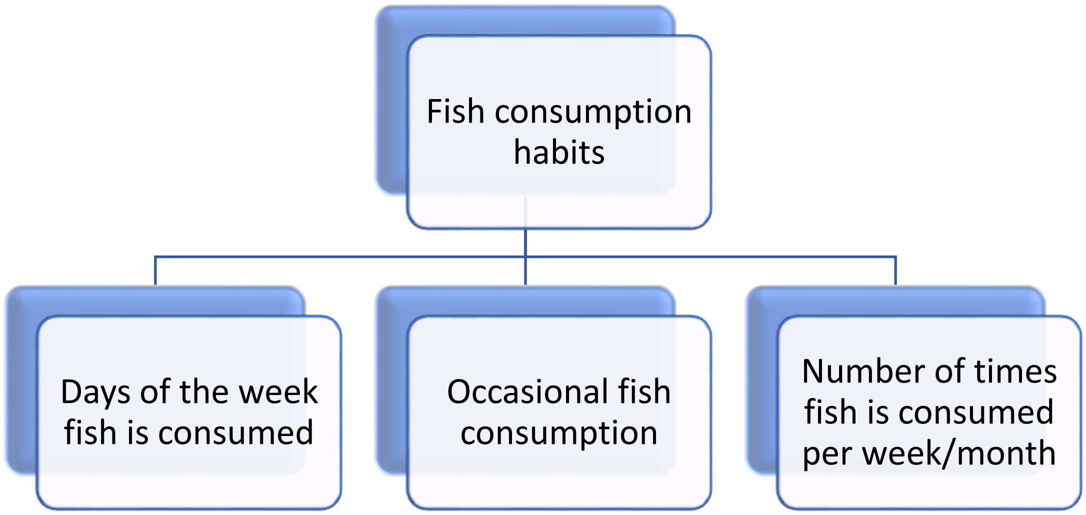


Figure 9.1: Thematic map showing the subthemes emerging from the participants fish consumption habits

Subtheme A- Occasional fish consumption

Two of the participants acknowledged that they occasionally consume fish.

"I am really a vegetarian. I do very occasionally eat fish, but it is very occasional. If I do eat it, ………, but I am not particularly fond of fish, I rarely eat it." P5 FG1

"I don't eat fish. I rarely eat fish. I don't particularly like fish. I don't dislike it. But I never had the opportunity of eating it, instead I do actually think of getting it." P3FG1

Subtheme B- Number of times fish is consumed per week/month

Participants acknowledged the different number of times that they consume fish per week/month. Some of them revealed that they consume fish once twice a month, at least once twice a week, once within one week, three times a week, four times a week, twice three times a week and sometimes every day. Some of the participants acknowledged that fish can be consumed anytime as long as a good diet is achieved. Below are some of the participants' comments:

One of the participants commented

"You know there are different ways of eating fish. So, I will say at least once possibly twice a week as for me." P5 FG2

Other participants acknowledged that

"I eat tinned mackerel at least probably once a week; I will eat tinned salmon probably once twice a month." P1 FG2

"I have fish twice may be three times a week." P1 FG1

"I love fish, but I don't have menu of what I eat. It can be once a month, it can be once in two months, it can be once within one week." P6 FG1

"Well eating fish as in fish just a plate of fish. I think it is comfortable for once a week, otherwise like me I eat something every day and there is a bit of fish in it. But if I have to have it as a plate once a week is ok." P6 FG1

Subtheme C- Days of the week fish is consumed

Fish was consumed by some of the participants on a Friday because it is a doctrine that was imbibed into them by their parent from childhood. It is also the norm of some religious organisation on their followers.

One of the participants stated

"In my house is a stock cupboard items tinned fish and fresh fish we usually have it and is quite possible that we are going to have it on a Wednesday and Friday simply because we have a guest on Wednesday night every week." P5 FG2

Another participant stated

"… I like big fish mackerel. Yes, that is my oily fish and from childhood my religion is catholic and always we have fish on Friday. So, it stays with you." P5 FG2

9.4.2.2 *Theme 2. Perceived enablers/barriers of fish consumption*

This theme explores the participants' perception about the enablers/barriers of fish consumption. This is subdivided into four main subthemes.

A. Individual enablers/barriers of fish consumption
B. Environmental enablers/barriers of fish consumption
C. Living in the Mediterranean/coastal area
D. Childhood/family with children influences on fish consumption

Figure 9.2 shows the thematic map of the sub-themes emerging from this theme

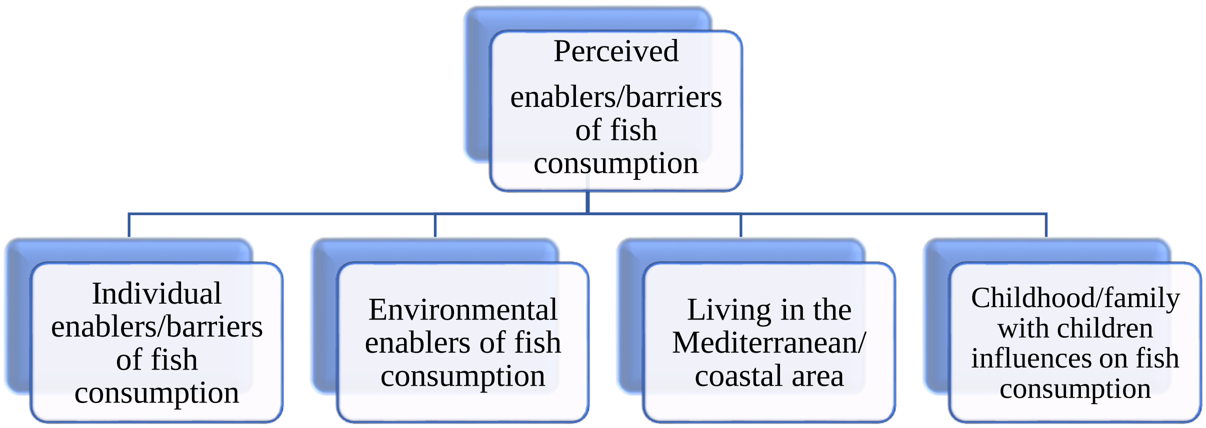


Figure 9.2: Thematic map showing the subthemes emerging from the perceived enablers/barriers of fish consumption

Subtheme A- Individual enablers/barriers of fish consumption

This phase of analysis explores the participants' views about the individual enabling factors that enhance their level of fish consumption. Most of the participants acknowledged various individual enabling factors that influence their rate of fish consumption. Some of these enabling factors include flavour, taste, variety, choice, believe, preference, love/enjoy eating fish, awareness, education/knowledge, marital status. Although several enabling factors were mentioned, participants also acknowledged some perceived barriers to fish consumption that include difficulty during fish preparation and bony or scaly fish as factors that hinder the way they consume fish. The majority of the participants believe that all the aforementioned factors play a positive or negative role in the way fish is consumed. Below are some of the participants' responses:

Subtheme-Enablers of fish consumption

Sub-subtheme A.1- Flavour

Flavour was considered by the participants as one of the crucial factors that enhance their level of fish consumption. One of them stated: *"I have always thought is a very lovely flavour with different fish, very lovely flavours" P2 FG1*

Sub-subtheme A.2-Taste

The participants perceived taste as a very important factor that allows and influence their rate of fish consumption. One of them commented: *"The taste is good. That is what we are sure of. The other things are not sure." P6 FG1*

Another participant reiterated that

"They are lovely food to eat, and so the taste from fish is very important, that is why I enjoy eating fish…." P2 FG1

Sub-subtheme A.3- Preference

Most of the participants believed that preference is one major factor that influences their fish consumption habit. One of the participants specified that *"I think it depends on preference of the individuals." P2 FG2*

On the other hand, another participant acknowledged that diet preference could be a barrier to fish consumption. This could be related to dislike for fish:

"… Like you said is your diet preferences. If you don't like fish, that can hinder you from buying the fish. So, you need to change your diet, … preferences to incorporate this." P6 FG2

Sub-subtheme A.4- Believe

Believe was mentioned by one of the participants as an influencing factor that could enhance the way fish is consumed. Believing that fish could be beneficial to one's health is very important. The participant commented:

"The believe that fish will do something positive to my life, that believe alone is pushing me to great change. Yes, and if am seeing the result, I am a channel to you know divert the news to other people. Anybody around me I tell them look I believe that fish can do this and do this for you, do the way am doing.…… So, the believe I got from the discussion we are having, I believe it will help me and it is helping me…. I think peoples believe is also important." P4 FG2

Sub-subtheme A.5- Variety

According to the participants the desire to consume variety of food is an important factor that influence the way they consume fish. Variety was also considered by other participants as consuming different types of fish. One participant stated:

"I eat fish because I believe in eating various diets and fish is part of them and that is the main reason why I eat fish. Not for actually any other purpose other than just to eat various diet." P1 FG2

Sub-subtheme A.6-Convenience

The convenience of having ready-made frozen fish available in the freezer makes the preparation of fish easier and faster. One of the participants acknowledged:

"Well like I said it is convenient sometimes. I love to have it fresh. So, all my fresh ingredients are in there. So, I get frozen. You can buy some frozen stuffs from Iceland which is very good, and then cut the seafood and include it all in one...... Is very convenient." P3 FG2

Sub-subtheme A.7- Love/like/ enjoy eating fish

The analysis of participants' views acknowledged that the enjoyment derived from eating fish influence and enhances its frequent consumption. One of the participants stated

"I have always enjoyed eating fish, and I have never had any ill effect from eating fish." P2 FG1

Another participant also believed that the likeness/love of eating fish does enhance the rate of fish consumption.

"What you like is the main one. If you like fish, you can eat more fish and if not, as we will say, if you all agree, you all like it as well, you all have the opportunity to have this fish as much as often. But if you don't like fish, that is if somebody doesn't like to prepare or doesn't like cooking fish, then you get problem all the time" P3 FG2

Subtheme-Barriers of fish consumption

Sub-subtheme A.8-Marital status

Most of the participants perceived marital status as one of the influencing factors that can enhance/hinder their level of fish consumption. They believe that being married and having a wife that is passionate about the preparation of fish can enhance the level of fish consumption in a home. One of the participants commented:

"if you have a wife who is not ready to prepare the fish, so it means you may be eating it when God permits. That is once in a year, once in a month, or once in a week. If you get a wife who is passionate in making fish, it means it will influence the number of times you eat fish. Yes, I think marital status is also important" P4 FG2

On the other hand, another participant believes that marital status cannot influence the way fish is consumed. He believes that fish can still be eaten if desired irrespective of being married or single.

"I don't think that would, I mean obviously that would be a practicality thing. If everybody is eating the same thing then is easier to put down the costs you buy one, then you can cook for everybody…. As in I don't think being single make any difference to me." P3 FG2

Sub-subtheme A.9- Awareness raising

Out of all the factors mentioned during the discussion, some participants believe that raising awareness through education/enlightenment could influence the way fish is eaten, while others disagreed. They claimed that people can be educated but might still not eat fish. Therefore, education or no education, some people just like fish and that makes them to consume it. Below are some of the participants' responses:

"No, I don't think education will make any difference on environment. It is what you prefer, what you taste, what you like is the main one. If you like fish, you can eat more fish, and if not, as we will say, if you all agree, you all like it as well, you all have the opportunity to have this fish as much as often. But if you don't like it, like we say somebody doesn't like to prepare or doesn't like cooking it, then you get problem all the time." P3 FG2

On the other hand, one of the participants commented:

"I can put my argument into two, because one is enlightenment, which is education. People who are educated can realise directly from their readings of the experiences of the benefit of eating fish that it will help during their old age. On the other hand, I will argue that people who are not even educated may say ok because I like it…., so I eat fish because I like it. Even in my own case education or no education, I like fish because I like fish." P6 FG1

Another participant acknowledged that educating children at a very young age could enhance their frequency of fish consumption. Participant commented:

"When we are talking about something with a young family, it is very important to introduce because you have got children that will say I don't want that. I don't want the fish in the fish and chips. They don't want fish and parsley sauce. They don't want different kinds of fish and I think is very important at an early stage, or earlier age to try and direct them or educate them into knowing how good fish is to them." P5 FG2

Sub-subtheme A.10- Knowledge

Some of the participants emphasised that having knowledge about the importance and benefit of eating fish could boost the way fish is consumed. One of the participants commented:

"I think knowledge is also important. For instance, somebody in the village, who is not educated eat fish because it is available without even knowing what it is giving him or her. But somebody who is educated like you know you are making this research and you found out that fish will give you this type of thing in your body, I don't think you will leave fish. You will continue to eat it, because of the knowledge of what it can do for your body. I think knowledge is also important." P4 FG2

Another participant also commented:

"Knowledge is also important because if you know it is good for you, you are going to buy more and introduce it into your diet. If you have knowledge obviously it does helps. You can say okay let me try it and that will enable you to introduce fish more into your diet." P3 FG2

Sub-subtheme A.11- Difficulty during fish Preparation

One of the participants believed that if any difficulty is encountered during fish preparation it could hinder the frequency of fish consumption. This shows how crucial self-efficacy is in enhancing the successful preparation of fish and improving fish consumption. The participant acknowledged

"… I think the ease of preparation can also hinder somebody. You know because some fish are very complicated very difficult to handle. So, some people may even though they like it, but they keep it on the other side and the choice. Some fish you don't really like them when they are prepared and some of them are tastier. So, I believe ease of preparation, the taste and peoples' choice are also important …." P4 FG2

Sub-subtheme A.12- Type (Bony or Scaly) fish

One of the participants believed that a bony or scaly fish could negatively influence the way fish is consumed, because of the risk of choking. The participant stated that *"The type of fish for me can hinder me from eating fish. Sometimes I eat fish that is skin have a lot of scale or what do you call it, Bony yeh, so I have the risk of choking. So that will discourage me forever for a very long time." P6 FG1*

Sub-subthemes A.13- Smell of fish

Analysis of the participants view shows that the smell of fish could be a barrier that affects the preparation and consumption of fish. One of the participants commented *"I find with the oily fish that it causes a lot of smell in the kitchen." P2 FG2*

Subtheme B- Environmental enablers/barriers of fish consumption

This phase of analysis explores the participants' views about the environmental enablers/barriers of fish consumption. These include availability, accessibility, income, and cost. Below are some of the participants' responses:

Sub-subtheme B.1- Availability

Availability was referred to as an enabler as well as a barrier to fish consumption by the participants. Participants believed that availability of fish in relation to getting easy access to fresh fish and tin fish could influence their fish consumption level. One of them stated

"I will go with availability…... most definitely. But I have got a question point, and I suppose possibly you would like to eat that day, and well availability is huge. Everyone can run out and buy a tin of tuna and probably put it into a sauce and have that…. Availability and…...will be huge factors." P1 FG2

Sub-subtheme B.2- Accessibility

Participants acknowledged that living too far from where fresh fish is sold could be a barrier to its consumption:

"……if you are talking of fresh fish. It could be really quite tricky. If you live, I don't know 5miles out of Wolverhampton and you don't have a car, yes to get fresh fish could really be quite a problem that could be top problem I think if you must separate them with the cost as well. So, availability of fresh fish is important." P2 FG2

Some participants on the other hand acknowledged that having a fish market closer to where they live make it easier for fish to be purchased at their convenience:

"……. if you got a fish monger down the road you going to just go there every day to get some fresh fish." P3 FG2

Sub-subtheme B.3- Cost

Cost of buying fish was perceived by some participants as cheap thereby enabling easy purchase of fish, while other participants perceived fish as very expensive when compared to other sources of protein, thereby hindering their purchasing power. Therefore, cost was perceived as an enabler as well as a barrier of fish consumption. Below are some of the participants' responses

"Cost is a big one I think……. Is income as well……I think fish can be very expensive sometimes, especially salmon and other fishes can be more expensive…. I think the cost is a big one." P3 FG2

Other participants emphasised that *"Fish is expensive even in Galway fish is expensive. When you pay 12 pounds for a piece of fish in size, you will get a lot of chicken for half that price." P1 FG2*

"Cost will be one of the hinderance, because if you don't have the money you can't afford to buy as often as you wish." P3 FG2

On the other hand, another participant responded

"I do remember as a child, I was born just at the end of the world and I could remember …. We had fish. Fish was cheap then, was very cheap……. almost every day that was our diet fish." P4 FG1

Sub-subtheme B.4- Income

Income was mentioned as one important influencing factor for fish consumption. Some of the participants had the opinion that irregular source of income or lack of adequate income could impact on the purchasing power of fish, thus influencing the type to buy and the frequency of fish consumption. One of the participants acknowledged that

"I have never had a problem of income in this my own world. My philosophy tells me that when I want to eat something I like; I don't look at my purse. I will rather buy less cloth but best of fish." P6 FG1

Another participant agreed that income is a very crucial factor to consider before fish can be adequately and satisfactorily consumed:

"I think income will be important especially some will have preferred oily fishes, you know, and they are very particularly expensive especially salmon, tuna, fresh tuna, so income will be important." P2 FG2

Subtheme C- Living in the Mediterranean/coastal area

Two of the participants mentioned that being born and having lived most of their life in the Mediterranean/coastal area influenced the rate at which they consume fish. One participant mentioned that

"I can eat quite a lot of fish. It is a factor of the Mediterranean as well." P3 FG2

Another participant responded

"I grew up and I live for the last 20 years in Galway, which is exactly on the coast such as coastal dam and I am not sure whether people eat more fish then, than they did now. Ok when the mackerel on the shores of mackerel comes out, people will go out fishing." P1 FG2

Another participant commented about how dwelling on seashore can positively influence the frequency of fish consumption:

"Is almost proven that when people live near fish you know on a lake shore or on a seashore, they are healthier, but with a fish diet. I mean Eskimos they just, they don't have any option they just eat raw fish, and they are fine." P2 FG2

Subtheme D- Childhood/family with children influences on fish eating

Some of the participants highlighted that the presence of children in the family could enhance and influence the way fish is consumed. One of the participants responded:

"I guess with the children around, young children fish and chips in the consumption might increase. It might influence increase in family fish consumption because of children." P4 FG1

Some of the participants mentioned that their childhood experience of fish consumption enhances and influence the way they consume fish at adulthood. Two of the participants commented

"In my diet as a child, I always had fish in my diet. So, I have always loved it as a child." P3 FG2

"I like big fish mackerel. Yes, that is my oily fish from childhood." P5 FG2

9.4.2.3 *Theme 3. Perceived Benefit of Eating Fish*

This theme highlights the perceived benefit of eating fish that was mentioned by most of the participants during the discussion. The four main subthemes identified are:

A. Attribute of fish consumption
B. Fish consumption reduces health problems
C. Fish consumption reduces dementia risk
D. Fish consumption and its relation to health

Figure 9.3 presents the thematic map showing participants' perceived benefit of eating fish

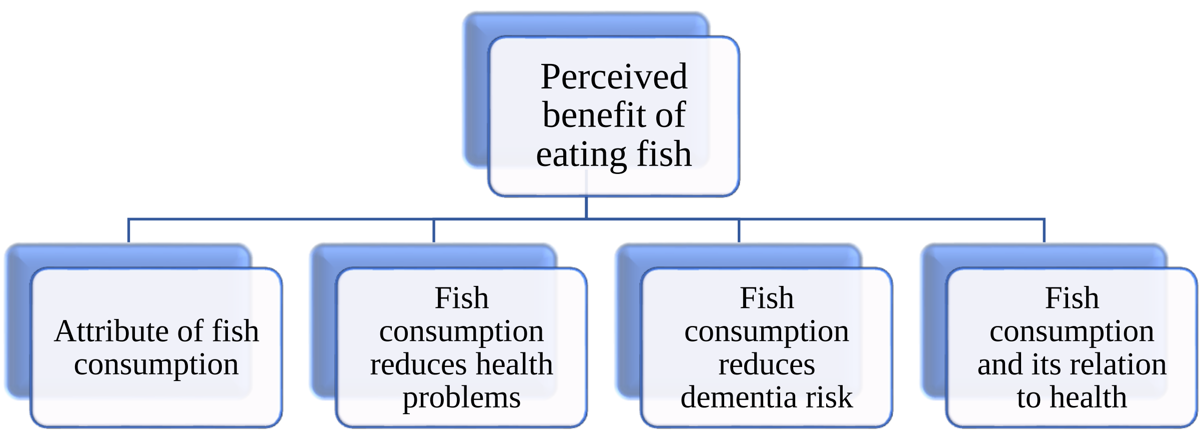


Figure 9.3: Thematic map showing the subthemes emerging from the perceived benefit of eating fish

Subtheme A- Attribute of fish consumption

Majority of the participants acknowledged the attributes of fish that makes it good for peoples' consumption. Some of them mentioned that fish is a good source of omega-3 fatty acids, a good source of protein, easy to digest, easy to chew, not fatty, and enhances memory. One of the participants commented

"Fish is good for old people for everybody especially for the aged people. One of the reasons I believe fish is good is because fish is not fatty, and whenever old person, person of certain age goes to the hospital or doctor one of the first things they check is their weight. So, they will ask them to be careful with their weight and then being careful involve not taking things of fatty food, so fish is one of the things that doesn't contain fat. It is not hard to chew for those who don't have teeth. Is not hard to chew, is not hard to digest, so therefore helps the brain." P4 FG2

Another participant commented

"There is some evidence to say that oily fish does help with memory." P1 FG2

Subtheme B- Fish consumption reduces health problems

Analysis of the participants views reflect that majority of the participants agreed that fish consumption can reduce health problems. One of the participants stated

"You know the benefit is like blood pressure, you know cholesterol, all those things will help from eating fish." P3 FG2

Other participants commented

"we really believe unless proven otherwise that fish help you know the problem of dementia even sight, eyesight, weight loss, or weight control, fish is involved." P4 FG2

"Yes, fish as we know contains a lot of other ingredient like they say iron something like that which all of them put together is a supplement. We don't have to believe that fish is medicine is not medicine. It is a supplement, and this is part of the things that help. They help the body to build up including the brain, the eye and so on and even the bones. So, it has all this benefit I believe." P4 FG2

"I know the people who are in …. Addition programmes following heart surgery, and pass the dietary advice given by dietician. They are absolutely being told to eat sufficient fish, so I absolutely think that there is CVD benefit to fish consumption." P1 FG2

Subtheme C- Fish consumption reduces dementia risk

Analysis of the participants views reveals that some participants believes that fish consumption can help with dementia problem by psychologically feeling good and happy when eating fish, while other participants are not totally sure if it helps. Below are some of the participants' responses:

"A lot of health benefit. Dementia is the target of everybody and fish, so we really believe unless proven otherwise that fish help you know the problem of dementia." P4 FG2

"It definitely helps dementia. …… that is the feeling around people that fish does help your brain, particularly oily fish is good." P5 FG1

One of the participants acknowledged that the good feeling gotten from the consumption of fish could also help to reduce the risk of dementia. He stated

"… Psychologically he feels good; he feels happy eating fish…. O yes But I think that is important. if you are feeling good and feeling happy you are not feeling stress eating fish, and I think may be the risk of going into a sort of you know dementia state will be lesser, maybe I think so I think that sort of feeling good is important." P4 FG1

Conversely, other participants commented

"Well, I am not sure, how useful it is for the risk of dementia. My mother had Alzheimer's and from being very young they were not short of money and they had fish. Growing up I did, growing up my husband did, and he had dementia from his 60's. My mother was in her 60's, early 60's." P5 FG2

"It is definitely good for your health and for your brain. Am pretty sure of that, because the research is done and for elderly people. But whether it helps with certain illness including dementia and Alzheimer's that is unclear. How much does it actually help to prevent or even get better or not certainly get better, but to prevent actually, because there is a lot of research that might consider that it could be hereditary the dementia regarding how much fish you eat. Is it truly you are going to get it regarding how much fish you eat, or you are going to delay getting it that could help as well? So, there are a lot of questions whether the maximum benefit you can get from a fish, is eating fish all the time. It definitely will be, it will be taken anyway regardless of what because there is still some benefit in it. That is my question, will it stop dementia, will it slow down dementia" P3 FG2

Subtheme D- Fish consumption and its relation to health

Analysis of the participants view shows that some of the participants are aware that fish consumption is related to health. One of the participants acknowledged

"Yes, is very good. But my suggestion is from what I read. There is a big correlation between good health and fish, between memory enhancement and fish, between dementia and fish. There is a big correlation." P6 FG1

9.4.2.4 *Theme 4. Commonly consumed fish*

This theme reflects the participants commonly consumed fish. These include two subthemes

A. Oily/Lean fish
B. Other fish types eaten

Figure 9.4 presents the thematic map showing participants commonly consumed fish

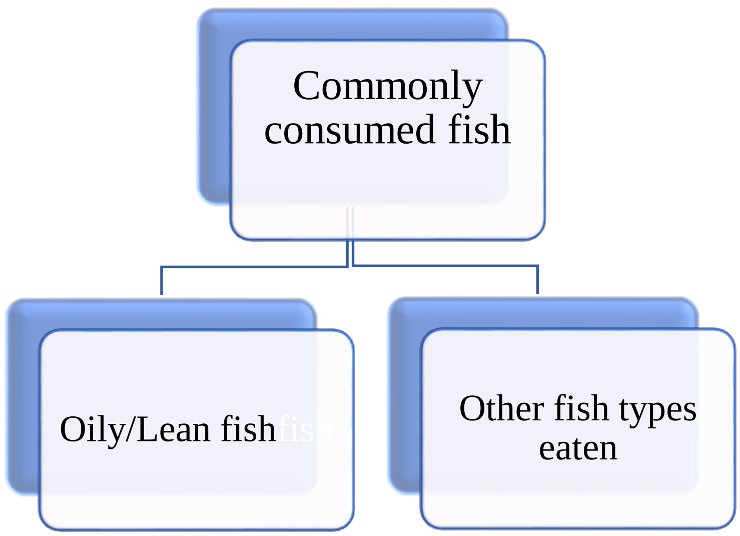


Figure 9.4: Thematic map showing the subthemes emerging from the participants commonly consumed fish

Subtheme A- Oily/ Lean fish

The analysis of participants views reflects that majority of the participants consume both the oily and lean fish. Below are the participants' responses.

"I suppose the main mackerel and salmon, prawns I do like prawns, and may do cod as well, but mainly probably oily fish." P1 FG2

"I do oily fishes. I do like kippers…. salmon, and tuna. So those are my three main oily ones, and then obviously I got cod, haddock, plaice and then you get seafoods like prawns, mussels." P3 FG2

"I eat both. I eat lesser oily than normal fish but will like to eat more oily fish for specific reason." P6 FG2

Subtheme B- Other fish types eaten

Some of the participants acknowledged that they consume seafoods (prawns, crayfish, and mussels) and other types of fish like stock fish. One participant commented

"We like fish, shellfish as well, prawns, mussels, crab, anything like that, and we like sea food…. We love eating a lot of pasta as well, with a lot of seafood in it." P3 FG2

Another participant stated

"Yes, in all, if we include some other types of fish. I eat some other types even without knowing, because crayfish is fish, stock fish is fish, then I eat fish, because we use it to make our soup. We use crayfish a lot, as we use stock fish as well." P6 FG1

9.4.2.5 *Theme 5. Participants concerns*

This theme reflects the two different concerns raised by some of the participants about fish consumption. The two key concerns raised in this study will be discussed under two subthemes. These include

A. Process of fish production
B. Misconception about frozen fish

Figure 9.5 shows the thematic map illustrating the participants' concerns about the consumption of fish

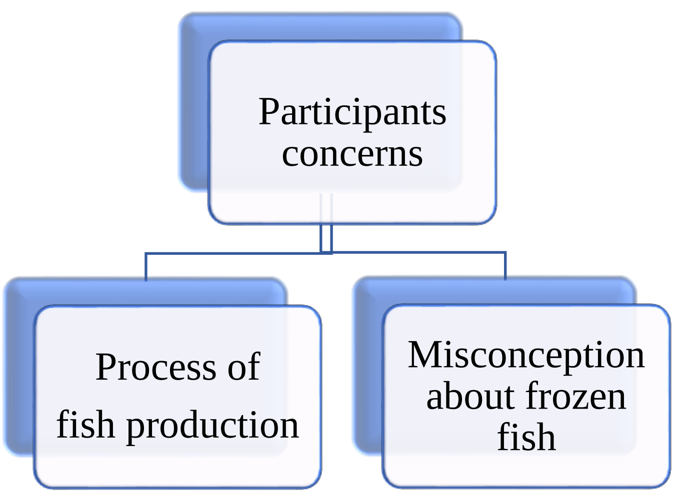


Figure 9.5: Thematic map showing the subthemes emerging from the participants' concerns about fish consumption

Subtheme A- Process of fish production

The analysis of participants' views shows the concerns raised by some of the participants regarding the production of fish. One of the participants was really concerned about how to differentiate the properly produced fish from the badly produced ones available in the market. The participant commented

"We don't really know exactly what we eat. This we call it what we eat, we don't know exactly how so the same thing with fish we are talking now, is just a topic. What we do what we eat that we call fish, sometimes they are not really fish. How do we identify what we are eating? Chinese can do whatever thing they like; they call it fish. It may be moving, but you know when we look at it, it is not fish. Is there any way we can get more study to know exactly what we eat, like when you buy chicken, if you see the production of chicken sometimes is all plastic all artificial, all these things are online? The same thing is with fish. Fishes are produced using chemicals. You put them today the next one week you sell them in the market. How do we identify what we eat what we call fish? I think this is a question as well as an issue for research" P6 FG1

Subtheme B- Misconception about frozen fish

Some participants have the notion that frozen foods are not fresh product. One of them commented:

"People get the misconception that frozen foods are not fresh, but actually it is the next best interest. It could be the next best interest. Even the cod that we get from there that we called the haddock, when we eat it, it looks like almost it comes from the sea. Frozen fish is fresher than the fish monger." P3 FG2

9.5 Discussion

This study explored the perception and views of older people on fish consumption and the risk of dementia and other health outcomes and the determining factors that can affect the consumption of fish. We identified and examined five overarching themes including perceived enablers/barriers of fish consumption, perceived benefit of eating fish, fish consumption habits, commonly consumed fish and participants' concern. The key findings of this study are discussed below, in relation to existing relevant literature.

9.5.1 *Fish consumption habits*

The fish consumption habits revealed in this study is consistent with the findings of two previous studies. A Belgium cross-sectional study found that fish consumption habit is a strong predictor of the frequency of fish consumption, and it is also a distinct factor that is embedded inside a set of items that measures perceived behavioural control (Verbeke and Vackier, 2005). This is supported by Juhl and Poulsen (2000) Denmark study that found a significant positive impact of fish consumption habit on frequency of fish consumption within the items in the measuring scales that was used to examine the antecedents of fish involvement.

9.5.2 *Perceived enablers/barriers of fish consumption*

The participants perceived enablers/barriers of fish consumption identified in this study is in accordance with an Australian systematic literature review of 14 articles, where price, availability and lack of confidence in seafood preparation were reported as barrier of fish consumption, while health, taste, and convenience were reported as enablers of fish consumption (Christenson *et al.*, 2017). The results also corroborate with another systematic review of 49 studies that acknowledged sensory perception, perceived health benefits, fish eating habits as very crucial enablers of fish consumption (Carlucci *et al.*, 2015). Also, this review acknowledged convenience perception, self-efficacy during fish preparation, high price and availability of fish, and inadequate knowledge to choose and prepare fish as key barriers of fish consumption (Carlucci *et al.*, 2015). All these factors could positively or negatively influence the way fish is consumed (Carlucci *et al.*, 2015).

9.5.2.1 Taste: In this study, the participants understood that taste is an important individual enabler or driver of fish consumption. This is consistent with the findings of previous studies that reported taste as one of the important enabling factors that influence the consumption of fish (Bredahl and

Grunert, 1997; Olsen, 2004; Verbeke and Vackier, 2005; Rortveit and Olsen, 2009; Birch *et al.*, 2012). Similarly, Brunsø *et al.* (2009) reported taste as a factor that drives the consumption of different food choices, thereby encouraging and enhancing the consumption of both fish and seafood. A systematic review of 14 studies by Christenson *et al.* (2017) also revealed taste as one of the important influencing factors that affect the consumption of fish and seafood.

9.5.2.2 Flavour: This study reported flavour as one of the important factors that enable the consumption of fish. This is in accordance with a US cross-sectional study of 1463 participants aged 18 to over 65 years old, where flavour was reported as one of the determinants that enhance the consumption fish (Kreider *et al.*, 1993).

9.5.2.3 Believe: This current study acknowledged believe as an individual enabling factor that affect the consumption of fish. This is evidenced as part of Carlucci *et al.* (2015) conceptual framework where believe was mentioned as one of the personal factors that influence the consumption of fish.

9.5.2.4 Variety: This study reported variety as an important individual enabler or driver of fish consumption. This is in accordance with previous studies that acknowledged the desire for variety of food as one of the important factors that influence the consumption of fish (Bredahl and Grunert, 1997; Rortveit and Olsen, 2009; Birch *et al.*, 2012).

9.5.2.5 Convenience: This study acknowledged convenience as one of the individual enabler of fish consumption. This is in accordance with previous studies that reported the convenience of having frozen seafood in the freezer as a factor that motivate a quicker preparation and consumption of fish (Jaeger and Meiselman, 2004; Mahon *et al.*, 2006; Brunso *et al.*, 2009; Birch *et al.*, 2012). Similarly, a qualitative study of 28 occasional seafood consumers in three European countries (Denmark, Iceland and Norway) reported convenience as part of the factors that positively influence seafood consumption (Altintzoglou *et al.*, 2010).

9.5.2.6 Marital status: In this study, marital status was perceived as an influencing factor that drives the consumption of fish provided the wife is passionate about fish preparation. This is consistent with previous studies. A cross-sectional study of 1200 participants aged 14-71 years in Taiwan by Li *et al.* (2001) reported that the unmarried participants have a reduced level of fish consumption. Similarly, Tanskanen *et al.* (2001) Finnish cross-sectional study of 3204 participants aged 25-64 years also revealed a lower consumption of fish among the unmarried participants. Thong and Solgaard's (2017) survey study revealed that being single has a negative significant impact on the consumption of three seafood products including fish which signifies that single consumers rarely consume fish compared to those that are married or living with families.

9.5.2.7 Knowledge/Education: In this study knowledge/education was reported as one of the crucial factors that enhance the consumption of fish. This is consistent with the findings of previous studies (Nauman *et al.,* 1995; Pieniak *et al.,* 2010). A European cross-sectional study of 4786 participants aged 18-84 years showed that participants that have better knowledge about fish, highly educated and interested in eating healthy are more likely to regularly consume fish (Pieniak *et al.,* 2010). Similarly, our result resonates with Barberger-Gateau *et al.* (2005) French cross-sectional study of 9280 participants aged ≥65 years that reported a significant increase in the consumption of fish as the level of education increases. Myrland *et al.* (2000) women study of 11000 participants aged 30-44 years also reported increase in fish consumption level among participants with higher level of education. However, our study results contradict other two findings that showed educational level as a non-significant predictor of fish consumption (Trondsen *et al.,* 2004; Verbeke and Vackier, 2005). The differences in the findings of the studies could be due to difference in cultural motivations of the respondents towards fish consumption, which could be due to living in the coastal regions.

9.5.2.8 Bony/scaly fish: This study participants reported bony/scaly fish as an individual barrier to fish consumption. This is in line with a Belgian cross-sectional study that reported bone as a factor that negatively affected the consumption of fish (Verbeke and Vackier, 2005). Other previous studies also reported presence of bone in fish as a barrier that affected the consumption of fish (Bredahl and Grunert, 1997; Oslen, 2004; Brunsø *et al.*, 2009; Rortveit and Olsen, 2009; Birch *et al.*, 2012).

9.5.2.9 Smell during fish preparation: Smell of fish that emerged as one of the barrier of fish consumption in this study is in accordance with McManus *et al.* (2007) qualitative study of seven focus group discussions where smell associated with fish was reported as a barrier that affected the consumption of fish. Smell was also acknowledged in Carlucci *et al.* (2015) systematic review of 49 studies as one of the sensory characteristics that influence the consumption of fish. Likewise, Brunso *et al.* (2009) qualitative study of six focus group discussions in two European countries (Spain and Belgium) acknowledged smell during fish preparation as a barrier that influence the consumption of fish.

9.5.2.10 Availability/accessibility: This study reported availability as one of the barriers that influence the consumption of fish. This is in accordance with previous studies. In an Australian qualitative study of 38 (7 focus groups) participants, McManus *et al.* (2007) reported availability/accessibility as one of the enabling factors that influence the purchase and frequency of fish consumption in the household. This resonate with Grieger, Miller and Cobiac (2012) cross-sectional study where availability was reported as a barrier for fresh, frozen fish and seafood consumption among 823 Australian lower fresh/finfish/seafood consumers. In a Norwegian women study of 9407 participants aged 45–69 years, lack of availability of fresh fish was also reported as a barrier of fish consumption (Trondsen *et al.*, 2003). Similarly, Birch *et al.* (2012) mixed methods research reported availability issue as one of the barriers that affect the purchase and proper consumption of fish.

9.5.2.11 Cost: This study participants reported cost as one of the barriers that affect the consumption of fish among older people. This is in accordance with an Australian cross-sectional study of 854 participants aged ≥51 years old where the cost was frequently reported as a major barrier for both fresh or frozen fin fish and seafood consumption (Grieger, Miller and Cobiac, 2012). Similarly Birch *et al.* (2012) mixed methods research of 60 (10 focus groups) and 1815 participants aged 18 to over 55 years reported cost/price as the most significant barrier that affected the purchase of both fresh fish and seafood with shorter shell life due to their expensive nature. In three focus group discussions study in three European countries (Denmark, Iceland, Norway), fish was perceived as very expensive by the participants which affected the way fish was purchased and consumed (Altintzoglou *et al.,* 2010). A Belgium cross-sectional study of participants aged 20-50 years also considered fish as a very expensive source of protein, which impact negatively on the participants' frequency of fish consumption (Verbeke *et al.*, 2008). Other studies also acknowledged cost/price as a very important barrier that affects the consumption of fish (Kreider *et al.,* 1993; Trondsen *et al.,* 2003; Olsen, 2004; Verbeke and Vackier, 2005; McManus *et al.*, 2007; Brunso *et al.*, 2009; Neale *et al.*, 2012; Thong and Sagaard, 2017). On the contrary, seafoods that are considered inexpensive are perceived as an enabler of fish consumption (McManus *et al.*, 2007; McManus e*t al.*, 2012), although cost/price was often referred to as a barrier of fish consumption.

9.5.2.12 Income: In this study, income was reported as an influencing factor that can positively or negatively affect the consumption of fish. This is in line with Can, Günlü and Can (2015) Turkish cross-sectional study of 127 participants that reported income as the most significant determining factor that influence fish consumption. This is supported by Thong and Sagaard's (2017) study of 966 adults in France that found household income as a significant barrier that affected the consumption of fish and shrimp. Our result also corresponds with Barberger-Gateau *et al.* (2005) cross-sectional study of 9280 participants aged ≥65 years that reported a significant increase in the consumption of fish among frequent fish consumers with increased in level of income. In Verbeke and Vackier (2005) Belgium cross-sectional study of 429 participants aged ≤25 to over 55 years old, infrequent fish consumption was found among participants with lowest income level. In contrast, a Nigerian cross-sectional study found that the higher the participants' level of income the less they spent on fish products, thereby lowering their level of fish consumption (Adeniyi, Omitoyin and Ojo, 2012). This could be due to a preference for other expensive sources of animal protein in some populations.

9.5.2.13 Childhood/family with children: The participants' perception in this study that believed that childhood/family with children can positively influence the consumption of fish is consistent with the findings of previous studies (Trondsen *et al.,* 2003; Altintzoglou *et al.,* 2010; Thorsdottir *et al.,* 2012). A Norwegian cross-sectional study of 9407 female participants aged 45-69 years suggested that frequent fish consumption habit during childhood can create a constant and established fish consumption habit during old age (Trondsen *et al.,* 2003; Trondsen *et al.,* 2004). An Australian cross-sectional study of 899 participants aged 18 to over 55 years also reported that regular fish consumption during childhood is likely to create positive, familiarity and favourable attitude towards fish consumption during adulthood (Birch and Lawley, 2014). This is supported by Altintzoglou *et al.* (2010) qualitative study of 28 focus group participants where frequent consumption of fish during childhood influenced the rate of fish consumption at later life. These findings do not necessarily mean that at old age a person will automatically continue to consume the same amount of fish due to other factors that they might have encountered while growing up, which can negatively influence the frequency of consumption (Carlucci *et al.,* 2015).

9.5.1.14 Living in the Mediterranean/coastal area: This study revealed that residing in the coastal region have a positive effect on the way fish is consumed. This is in line with Trondsen *et al.* (2004) a Norwegian cross-sectional study of 9407 participants aged 45-69 years, where increased odds of fatty fish consumption was found among participants that reside in the eastern coastal region when compared to those that live in the eastern inland region. Similarly, Verbeke and Vackier (2004) Belgian cross-sectional study of 429 respondents aged 40.6 years reported that those participants that resided in the coastal region of West Flanders regularly consumed fish compared to those that resided in other regions of the country, indicating a significant effect of region on the frequency of fish consumption.

9.5.3 ***Perceived benefit of eating fish***

The perceived benefit of eating fish acknowledged in this study is consistent with the findings of several previous studies. A systematic review of 49 studies acknowledged perceived health benefits as a very crucial factor that influence and drives peoples' fish consumption habit (Carlucci *et al.,* 2015). These previous studies acknowledged that participants perceived fish and seafood as a beneficial healthy food due to their high level of protein, omega-3 fatty acids constituents and its reduced fat content (Verbeke *et al.,* 2008; Brunsø *et al.,* 2009; Burger and Gochfeld, 2009; Birch *et al.,* 2012; Grieger, Miller and Cobiac, 2012; Neale *et al.,* 2012).

9.5.3.1 Fish consumption reduces health problems: The result revealed the participants perceived believe that fish consumption reduces health problems. This was consistent with findings from previous studies where fish consumption was associated with reducing the risk of several health problems. An Italian Moli-sani cohort study involving 20,969 Mediterranean participants aged ≥35 years with a median follow up period of 4.3 years found a 40% reduced risk of CHD with HR 0.60 (0.38-0.94) among those participants that consumed fish ≥4times/week when compared to those with lowest fish intake level of <2times/week (Bonaccio *et al.,* 2017). Correspondingly, Hengeveld *et al.* (2018) found a reduced risk of ischaemic stroke among 34,033 Dutch participants aged 20-70 years that consumed ≥1servings per week of lean and fatty fish with HR 0.70 (0.57-0.86) and 0.63 (0.39-1.02) respectively, when compared with non-fish consumers. Varraso *et al.* (2014) Nurses' Health Study and Health Professionals Follow-Up study involving 120,175 male and female participants aged 30-75 years with a follow up period of 16 years found a 29% significant reduction in the risk of chronic obstructive pulmonary disease (COPD) with adjusted HR 0.71(0.54-0.94) when the highest fish consumption level of ≥4 servings/week was compared with the lowest fish consumption level of <1 serving/week. Verbeke *et al.* (2005) study also acknowledged that fish consumption reduces the risk of coronary heart disease and cancer.

9.5.3.2. Fish consumption reduces dementia risk: The qualitative analysis of participants views shows that fish consumption reduces dementia risk. This is consistent with previous quantitative studies that showed a reduction in the risk of incident dementia with frequent fish consumption (Kalmijn *et al.,* 1997; Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005; Barberger-Gateau *et al.,* 2007). A Rotterdam population-based cohort study of 5386 participants aged ≥55 years found a significant reduction in the risk of dementia among >18.5g/day fish consumers RR 0.4(0.2-0.9) when compared with the lowest fish consumers (Kalmijn *et al.,* 1997).

Similarly, the Three-city prospective cohort study of 8085 participants aged ≥65years showed a reduction in the risk of dementia among frequent fish consumers (Barberger-Gateau *et al.*, 2007). Our study and the earlier studies results differs from the result of another Rotterdam study of 5395 participants aged ≥55 years that found a non-significant association of higher fish consumption and the risk of dementia during a follow up period of 9.6 years (Devore *et al.*, 2009). The variation in the results of these studies could be due to the difference in their follow up period and the effect of reverse causation.

9.5.4 *Commonly consumed fish*

The commonly consumed fish highlighted in this study is consistent with those reported in other studies. Most of the previous studies reported fish including both oily and lean fish and seafood as the commonly consumed fish product (Trondsen *et al.,* 2003; Altintzoglou *et al.,* 2010; Grieger, Miller and Cobiac, 2012; McManus *et al.,* 2012; Thorsdottir *et al.,* 2012).

9.5.5 *Strength and limitations of the study*

The main strength of this study is using focus group design approach to explore the perception and views of older people on the association of fish consumption with the risk of dementia and the determining factors that can affect the consumption of fish, thereby allowing an in depth understanding of the 'what', 'why' and 'how' of a qualitative research as acknowledged in Sallis *et al.* (2006). The main limitation of this study is that due to the difficulty faced to get enough interested participants and the time constraint of the research, only two FGDs were feasible. Maybe having more than two FGDs could have provided a comprehensive exploration and deeper understanding of the topic of discussion. Nevertheless, having gone through adequate training to facilitate the two FGDs that took approximately 60 minutes each, this allowed the researcher to thoroughly facilitate and coordinate the two FGD sessions. This contributed to generating adequate, reliable, and quality data that emerge valuable themes and added to the understanding of the research topic. Secondly, the small, exploratory, and descriptive nature of this study limits the generalisability of its findings to the wider population, since the main purpose of the design is to generate a realistic data that shows a deeper understanding of the views and perception of the participants (Morgan, 1998; Maxwell, 2005) and not necessarily to generalise the findings (Krueger, 1998). Therefore, further studies that require the use of a larger number of focus group participants could further provide more detail evidence about the association of fish consumption with the risk of dementia and the determining factors that can affect the consumption of fish in older people.

9.6 Conclusion

This study revealed the perceived views of older people on fish consumption and the risk of dementia and the determining factors that can affect the consumption of fish. Participants acknowledged that they consume fish for its taste, flavour, the desire for variety of food and the nutritional and health benefit including reducing the risk of dementia and other health outcomes. The cost, bony/scaly fish and availability/accessibility of fish were identified and highlighted as the major barriers that affected the consumption of fish. Strategies needed to improve the consumption of fish/seafood must address and eliminate the barriers affecting its inadequate consumption to ensure a better quality, accessibility and price affordability.

CHAPTER TEN: GENERAL DISCUSSION

10.1 Introduction

This chapter highlights how both qualitative and quantitative key findings of this research are connected in relation to the research aims and objectives and supported by existing literatures. Previous studies on fish consumption and dementia risk were predominantly of quantitative design; therefore, a pragmatic approach with thematic analysis was employed in this research to carry out the investigation to bridge the gap in knowledge. This approach allowed thorough exploration and in-depth understanding of the impact of fish consumption on the incidence and prognosis of dementia and the determinants that could affect the consumption of fish using two different research designs. This chapter will begin by summarising the research findings, followed by showing how both findings are linked i.e. the integration of findings.

10.2 Summary of key findings

As the aged population grows, it is paramount to identify and implement the strategies needed to lessen the risk of dementia. This is important to maintain the cognitive wellbeing of the aged population, since there are presently no effective drugs to cure dementia and due to its profound influence on future healthcare costs, care home usage, caregiver burden and the overall quality of life (Andel *et al.,* 2005). To contribute to the body of knowledge of how modifiable dietary lifestyle factors such as fish consumption and the determinants that could affect its proper consumption influence the cognitive wellbeing of the aged, this thesis was conducted to examine the impact of fish consumption on the incidence of dementia and mortality in older people with dementia. It also aimed to explore the determining factors that can affect the consumption of fish in older people. All these were achieved by conducting a mixed methodological research through incorporating several study designs including a comprehensive systematic worldwide literature review and meta-analysis, one cross-sectional study, three cohort studies and two focus group discussions. Although our comprehensive systematic literature review in Chapter 4 revealed an association between fish consumption and the risk of dementia, the findings were inconsistent. We found that four of the studied populations reported a statistically significant association of fish consumption with reduced risk of dementia, although two of them (Conquer *et al.,* 2000; Tully *et al.,* 2003) did not present the effect sizes, while data from eleven studied populations showed an association but a non-statistically significant reduction, while two exhibited no association (or increased risk) (Albanese *et al.,* 2009; Devore *et al.,* 2009). These inconsistencies in the findings can be attributed to several methodological variances among the relevant studies. These include the type of fish consumed, duration of follow-up, dosage of fish consumption, adjustments for confounders, genetic susceptibility, measure of dementia, study population, sample size and reverse causation. The determinants of fish consumption in older people examined in Chapter 5 showed the inverse association of fish consumption with older age, female gender, smoking, living in a rural area, having educational level of ≤primary school, occupation of peasant, low income, financial difficulties, being never married/divorced, having undetected hypertension, depression and dementia. However, participants with central obesity and heart disease at baseline had increased odds of fish consumption. The results revealed that large socioeconomic inequalities and certain lifestyle, psychosocial factors and health-related conditions are strong determinants of fish consumption in older people. Targeting these high-risk groups of older people with low educational level, low-income level and living in a rural area for preventing low consumption of fish would increase their level of consumption. In Chapter 6, the meta-analysis of available data from the literature and the new Chinese cross-sectional study that examined the association of fish consumption with the risk of dementia found that fish consumption has a protective effect on the risk of dementia and AD; that is higher consumption of fish is associated with a lower risk of dementia with similar impact among countries with different levels of income. The result suggests that increasing fish consumption may help to prevent dementia worldwide regardless of income level. In Chapter 7, using a Chinese cohort dataset to examine the association of fish consumption with the risk of dementia revealed similar protective effect of fish consumption on the risk of dementia. In Chapter 8, the researcher investigated the impact of fish consumption on all-cause mortality in older people and examined differences in the impact between people with and without dementia. The findings reveal that increased consumption of fish in older people significantly reduced all-cause mortality with dose-response association, however, no significant association of fish consumption with mortality was found among subgroup of people with dementia. This result shows that fish consumption could not help to prolong life in people living with dementia. This beneficial effect of fish consumption on the risk of all-cause mortality was consistent with the findings of previous studies (Yuan *et al.,* 2001; Wang *et al.,* 2011; Zhang *et al.*, 2018). In Chapter 9, the two focus group discussions that explored the views and perception of older people on the association of fish consumption with the risk and mortality of dementia and the determining factors that can affect the consumption of fish identified five overarching themes. These include fish consumption habits, perceived enablers/barriers of fish consumption, perceived benefit of eating fish, commonly consumed fish and the participants' concern. Participants acknowledged that they consume fish for its taste, flavour, the desire for variety of food and the nutritional and health benefit including reducing the risk of dementia and other health outcomes.

Some of the qualitative findings were consistent with the quantitative findings of this thesis, thus providing triangulation between them. This will be discussed under the following headings adopted from Carlucci *et al.* (2015) conceptual framework on factors influencing the consumption of fish.

10.3 Factors influencing the consumption of fish in older people

In this current study, some of the perceived enablers/barriers of fish consumption experienced by older people in the qualitative findings resonate with some of the factors influencing the consumption of fish in older people found in the quantitative findings. These factors are discussed in the following sub-sections.

10.3.1 Personal (beliefs, attitudes and demographics) environmental and situational factors

Marital status: Marital status was considered has an influencing factor that affects the consumption of fish in both the quantitative and the qualitative findings of this study. The quantitative findings showed reduced odds of fish consumption among the 'Never married/Divorced' participants. This is consistent with the qualitative findings, where participants reported that marital status is an enabler/driver of fish consumption provided the wife is passionate about fish preparation. This result resonates with Thong and Sagaard (2017) study that showed that single consumers seldomly consume fish compared to the married or those living with families. This finding was in contrast with those of Can, Günlü and Can (2015) cross-sectional study that revealed a significantly greater yearly fish intake among the single compared to the married participants. The variation in the findings could be because those who were never married/divorced had a lower household income, and they may have fewer children at home which influence the demand for fish consumption.

Knowledge/Education: Knowledge/education was perceived as an enabling factor that can influence the consumption of fish in the qualitative findings, because educated people are exposed to the beneficial effect of fish consumption through public awareness, thereby enhancing their level of fish intake. This resonates with the quantitative findings, where older people with low educational level had low level of fish consumption. This is consistent with the findings of previous studies (Nauman *et al.,* 1995; Pieniak *et al.,* 2010; Barberger-Gateau *et al.,* 2005) where highly educated participants were reported to frequently consume fish. On the other hand, educational level was reported as a non-significant factor that influence the consumption of fish in both Trondsen *et al.* (2004) and Verbeke and Vackier (2005) studies. The differences in the findings could be due to the cultural variations in the way fish is consumed, which could be attributed to living in the coastal regions. The choice of consuming fish may be due to what is available to eat in poorer countries as compared to the relatively wealthy countries.

Income: In the qualitative findings, income was reported as an influencing factor that can positively or negatively affect the consumption of fish. This corroborates with the quantitative findings that found a significantly increase odds of fish consumption with increase in income level. This resonate with previous studies, where income was reported as the most significant determining factor that influence the consumption of fish (Can, Günlü and Can, 2015; Thong and Sagaard, 2017). Conversely, Adeniyi, Omitoyin and Ojo (2012) study found a lesser rate of purchase of fish products among the participants as their level of income increases, thus affecting their frequency of fish consumption. This could be due to a preference for other expensive sources of animal protein in some populations.

10.3.1.1 Environmental and situational factors

Living in the Mediterranean/coastal area: The qualitative findings of this study revealed that residing in the coastal region have a positive effect on the way fish is consumed. This is in line with Trondsen *et al.* (2004) and Verbeke and Vackier (2004) studies, where increased consumption fish was found among participants that reside in the coastal region when compared to those that live in the inland region.

Availability/accessibility: The qualitative findings of this study reported availability as one of the barriers that influence the consumption of fish. This resonates with previous studies that reported availability as a factor that negatively influence the consumption of fish (Trondsen *et al.,* 2003; McManus *et al.,* 2007; Grieger *et al.,* 2012).

10.3.2 Health beliefs

10.3.2.1 Fish consumption reduces dementia risk: The qualitative analysis of participants' views revealed the participants believe that fish consumption can reduce the risk of dementia. This is consistent with the quantitative findings of the meta-analysis of available data from the literature and the new Chinese cross-sectional and cohort studies that examined the association between fish consumption and the risk of dementia. The result shows that fish consumption has a protective effect on the risk of dementia and AD; that is higher consumption of fish is associated with a lower risk of dementia. This resonates with the findings of previous studies that reported that frequent fish consumption is associated with lower risk of dementia (Barberger-Gateau *et al.,* 2002; Morris *et al.,* 2003; Huang *et al.,* 2005). Conversely, no association of fish consumption on the risk of dementia was found in the Rotterdam cohort study (Devore *et al.,* 2009). This could be due to the reverse causation effect that resulted from the long-term follow-up period, thus affecting the frequency of fish consumption.

10.3.2.2 Fish consumption reduces health problems: The qualitative findings revealed that participants believe that fish consumption reduces health problems. This is consistent with the quantitative findings that showed that fish consumption reduces the risk of dementia and all-cause mortality. This corresponds with findings from previous studies, where fish consumption was associated with reducing the risk of several health problems (Bonaccio *et al.*, 2017; Hengeveld *et al.*, 2018).

10.4 Strengths and Limitations including Suggestions for Future Research

10.4.1 Strengths of the study

The main strength of this PhD study lies in its mixed methods of large-scale population-based health surveys, meta-analysis and focus group research to examine the association between consumption of fish and dementia. The large-scale population-based health studies consisted of a multi-centre cross-sectional study and a prospective cohort design with the long-term follow-up period, and their large sample sizes. The detailed confounding variables available also allowed us to comprehensively explore the role of fish consumption on the risk of dementia and all-cause mortality. The comprehensive search strategy employed in the systematic literature review allowed the accommodation of all the available evidence on the association of fish consumption and the risk of dementia. There were two focus groups run according to the standard methods. The mixed method approach adopted in this research, since previous studies on fish consumption and dementia risk were predominantly of quantitative design, also allowed thorough exploration and in-depth understanding of the impact of fish consumption on the incidence and prognosis of dementia and the determinants that could affect the consumption of fish.

10.4.2 Limitations of the study

Although all the studies in this thesis were effectively conducted and provided new insight into the association between fish consumption and the incidence and mortality of dementia, they have limitations that should be recognised. Firstly, in the studies, there may be a recall bias from the participants regarding fish consumption level that occurred during the interview. This could attenuate the associations that have been found. Secondly, more detailed information about the different types (e.g. lean, fatty-fish, fried fish and seafood) and quantity of fish consumed was not recorded and thus the inability to examine the consumption levels. This could have affected the inferences on the exact fish types and the risk of dementia and all-cause mortality. But generally, total fish consumption was inversely associated with the risk of dementia and all-cause mortality. There are few studies conducted to examine the association of specific types of fish with dementia incidence and all-cause mortality, and thus further research is required to ensure more informative public health recommendations are made to the populace. Thirdly, the inability to adjust for total energy intake in the data analysis of the health survey and cohort studies due to its absence among the variables assessed might have impacted on the overall results. Fourthly, in the qualitative phase of this study, the focus group discussions setting could have intimidated some of the participants, which might have affected the thoughts shared by them. In addition, the exploratory and descriptive nature of the focus group limits the generalisability of its findings to the research participants, since the main purpose of the design is to generate a realistic data that shows a deeper understanding of the views and perception of the participants (Morgan, 1998; Maxwell, 2005) and not necessarily to generalise the findings (Krueger, 1998). In addition, the fewer number of focus group sections might have impacted on the findings, since further exploration of the emergent themes was not possible due to limited study time. However, the adequate training received by the researcher aided the thorough facilitation and coordination of the two focus group discussions, which generated adequate, reliable, and valuable data that added to the knowledge and understanding of the research topic.

10.4.3 Suggestions for future research

Since there are presently no effective drugs to cure dementia, despite investment of billions of pounds on dementia treatment, the strategies developed to fight against dementia are now gradually tailored towards its prevention. Therefore, delaying the risk of dementia for some years no matter the percentage of people involved will be beneficial and of great achievement, thus allowing people to attain old age without developing the disease. This thesis was conducted to increase our knowledge and understanding of how fish consumption, a modifiable dietary lifestyle factor is associated with the incidence and mortality of dementia. Eventually, these and other related studies will drive and guide future studies that are designed specifically for older people to maintain cognitive health or delay the risk of dementia. Since higher consumption of fish could lower the risk of dementia and all-cause mortality, mechanistic research is necessary and important to elucidate the beneficial role that fish consumption has on the risk of dementia and all-cause mortality in order to improve life expectancy. This is to provide the highest level of evidence in determining cause-effect relationship and to elucidate how fish consumption; a dietary factor affects cognitive reserves. It is also advisable that future studies should include measures of brain imaging and biomarkers in their investigation to validate, describe and explain the structural and functional impacts of fish consumption on cognitive health. In addition, comprehensive experimental studies that require the use of laboratory and animal models are required to elucidate how the consumption of fish, its constituents and other dietary factors affect the brain at the neurophysiological level and their relation to neurodegenerative diseases. This is important since animal studies provide valuable information about the biological mechanisms of how the fish components and other food nutrients are related to cell function and neurodegenerative disease.

Presently, majority of the existing evidence that support the association of fish consumption with the risk of dementia and cognitive impairment are inclined towards the elderly. Due to the increase in the aging population as well as the associated increase in neurodegenerative disorders (e.g. dementia), it is paramount that future studies should continue to investigate the protective effect of fish consumption on the risk of dementia and AD among older people. However, it is necessary to conduct similar studies among healthy young and middle-aged adults who have different levels of fish consumption to investigate the association of habitual fish consumption with dementia, in order to establish a life course approach. This is important because cognitive development starts from a prenatal stage, while mid-20s mark the peak of individual cognitive capability and late-middle age indicates the start of cognitive decline, signifying a very delicate point to understand the cognitive pathway and start an intervention. Therefore, it is important that future research examining the association of any dietary factors including fish consumption with the risk of dementia and all-cause mortality are carried out using a life course approach (Baltes *et al.,* 1999; Whalley *et al.,* 2006; Anstey, 2014). This life course approach provides a significant opportunity to explain how fish consumption and other dietary factors influences the brain, since evidence has shown that early life is a very crucial period for the development of cognitive reserve (Stern, 2009). This is in order to achieve an optimal cognitive function later in life, since cognitive development is build-up overtime during both childhood and early adulthood, thereby unravelling the chronological order of these dietary factors (e.g. fish consumption) in relation to cognitive health and life expectancy.

Additionally, it is obvious that various measures (e.g FFQs, SFFQs) were adopted to quantify and assess the consumption of fish in all the studies assessed in the systematic review and meta-analysis, which could have possibly influenced and caused the variations in the findings.

Therefore, to increase the reliability and validity of this measure, a unified measure that report the rate of consumption in grams per day should be encouraged in future studies to enhance standardisation as well as to increase the reliability and comparability across relevant studies. Considering standardisation, future studies should ensure that all confounding variables or comorbidities such as cardiovascular risk factors and socio-economic status that could influence or affect the association of fish consumption and the risk of dementia are thoroughly assessed and reported.

It is also very crucial for future research to tailor their investigation towards the identification of those people predisposed to developing poor cognitive health in later life so that they can adequately benefit from the strategies identified as protective in this thesis. Other factors including non-modifiable risk factors associated with old age and cognitive decline should also be thoroughly examined alongside the modifiable dietary factors to enable prompt and early execution of strategies to ensure their effectiveness, thereby lowering the incidence of dementia. Future research should also endeavour to assess all the types of fish people consume in relation to their method of preparation to elucidate their association with the risk of dementia, since all type of fish have different levels of omega-3 fatty acid, a fish constituent that is mainly the protective nutrient for neurodegenerative disorder. In addition, future longitudinal research should make effort to measure dietary exposure at various time points, since majority of the previous studies did not consider the differences in the dietary exposure over a long-term period. Future research should also attempt to elucidate the impact of gender difference on the association of fish consumption and the risk of incident dementia and AD, since the information available on this relationship is limited in previous studies.

Overall, the strategies for future dementia research should endeavour to focus on addressing the best window period that is ideal in peoples life to achieve an effective dementia prevention, find ways and approach to encourage and motivate people towards a healthy lifestyle including eating a balanced diet in addition to the consumption of fish, engaging in regular exercise that help in stimulating the brain, identify and tackle methodological challenges of interventional studies, facilitate international collaboration among researchers through knowledge dissemination and ensuring research findings are transformed into effective public health promotion for adequate implementation and to achieve a positive impact. In addition, future research should endeavour to examine the association of increased fish consumption with incidence dementia in a long-term follow-up period of $\geq$10 years to rule out the possibility of reverse causation that could have an impact on the dietary habits of the participants in short term follow-up studies.

10.4.4 Summary

Overall, the studies in this thesis suggests that fish consumption, a modifiable lifestyle dietary factor can positively influence the cognitive wellbeing and life expectancy of the aged population. Three of the studies provided an insight into how higher consumption of fish is associated with lower risk of dementia and all-cause mortality among older people, thereby helping to prevent dementia worldwide regardless of income levels and increasing life expectancy. The findings also provided an insight into how nutritional status regarding the consumption of inadequate fish protein among older people can be affected by sociodemographic and health factors. The qualitative phase of this thesis provided a new insight into the views and perception of older people on fish consumption and the risk of dementia and other health outcomes as well as the determining factors that can affect the consumption of fish. The findings of this thesis have implications for the field of dementia prevention and the recommendations for future research are discussed in the next session.

10.5 Implications of Findings and Recommendations

10.5.1 Implications of Findings

The studies in this thesis have illustrated the possible association of the consumption of fish with the incidence and mortality of dementia and identified the determinants that could affect the consumption of fish in older age. This thesis has demonstrated the beneficial effects of eating fish on reducing the risk of dementia and all-cause mortality. The epidemic of dementia has become a public health problem worldwide. As the world population, has been ageing, the number of people with dementia will continue to rise. Most of the increment is expected to be in LMIC, which currently hold 58% of people living with dementia, with further increment by the year 2050 (Prince *et al.*, 2015). In China, there is a growing number of people living with dementia due to the population of older people with mixed characteristics (e.g. low level of education but rapidly increased income) (Chen *et al.*, 2012). This thesis demonstrated a significant association of higher fish consumption with reduced risk of dementia, which further indicates the potential importance of consuming fish in preventing dementia worldwide. At present, global per capita fish consumption level is estimated to be on average 20 kg/year (FAO, 2016) and is lower in LMIC (18.8 kg/year) than in high-income countries (26.8kg/year). This study demonstrated consistent findings of the impact of fish consumption on the risk of dementia between LMIC and high-income countries. People should thus increase their level of fish consumption, especially in areas where the consumption is quite low such as LMIC, to reduce the burden of dementia. Also, people living in high income countries, including the UK, should be informed of the beneficial impact of fish consumption to further increase its intake.

In addition, this thesis offers an insight into how the nutritional status regarding the consumption of inadequate fish protein among older people can be affected by sociodemographic and health factors. There is evidence that no or inadequate consumption of fish could impact on individuals' cognitive function and increase the risk of cardiovascular disease (Larsson and Orsini, 2011; He *et al.*, 2004) and dementia (Bakre *et al.*, 2018). This result can help the government in their public health policies decision making. This could assist in channeling their resources towards availability and affordability of fish among socio-economically-deprived older populations. Boosting the economy income level through job creation and increasing social welfare might also enhance their overall food intake level including fish consumption, since food cannot be eaten in isolation, thus having a positive impact on their health and well-being. Facilitating the preparation technique of fish could also ease the stress displayed during cooking through provision of ready-made boneless fish products that is accessible to purchase in the market. This would be especially for the high-risk groups with inadequate consumption of fish, including older people with depression and dementia. Overall, strategies needed to improve the consumption of fish/seafood must address and eliminate the barriers affecting its inadequate consumption to ensure better quality, convenience, availability, accessibility and price affordability.

10.5.2 Recommendations

If a modifiable lifestyle dietary factor such as fish consumption have positive impact on preventing the risk of dementia, such findings are crucial. Healthcare professionals across various settings can utilise the knowledge of the protective effect of fish consumption in promoting the health of older people by encouraging adequate consumption of fish and other healthy dietary factors (e.g. fruit and vegetable intake) for optimum protection of brain health of older people.

Regular and free routine health check and proper assessment of older peoples' cognitive status will allow early detection of those undergoing neurodegenerative changes, thereby ensuring that necessary intervention including fish consumption is tailored towards reducing the risk of progression into dementia. This intervention could assist in reducing the costs associated with caring for people living with dementia and thus reducing its prevalence. Additionally, this will help to reassure the affected people that the cognitive changes are a normal part of the aging process.

Medical practitioners should encourage people to modify or adopt healthier lifestyles including increased consumption of fish from early to late life since this could help in reducing the risk of dementia and the risk factors associated with the disease. Public health campaigns that promote healthy lifestyle modification in reducing the risk of dementia must be encouraged and propagated among the populace through mass media campaigns.

Future public health research and policy must target other risk factors associated with dementia (e.g. CVD) that could also affect the health of older people, to promote the prevention of dementia. Overall, with an increase in the aging population, identification and implementation of strategy to enhance individual cognitive ability is paramount for proper cognitive maintenance throughout the life course.

10.6 Conclusions and Contribution to Knowledge

10.6.1 Introduction

This chapter presents the conclusion of the entire study. This is divided into separate sections that include the overview of the research, followed by the answers to the research questions. This chapter also presents the contribution to knowledge and finally the conclusions of the study.

10.6.2 Overview of the Research

This thesis employed a mixed method research design that started with a quantitative phase followed by the qualitative phase. The data analysis was conducted utilising the Chinese multi-provinces cohort dataset of 6071 participants aged ≥ 60 years to examine the factors influencing the consumption of fish in older people and to assess the associations of fish consumption with the risk of dementia and all-cause mortality, through multivariate adjusted logistic regression models and the Cox proportional hazards regression models, respectively. Subsequently, a semi-structured discussion guide was developed for the collection of the qualitative data in the UK using two focus group discussions of six participants each and the data were analysed using thematic analysis, after which both results were integrated at the discussion stage. This thesis presents six independent studies including three cohort studies that examined the determinants of fish consumption in older people and evaluated the association of fish consumption with dementia risk and all-cause mortality among older people with and without dementia; a cross-sectional study that assessed the association between fish consumption and the risk of dementia; a new comprehensive systematic worldwide literature review and meta-analysis examining the association between fish consumption and the risk of dementia, and two focus group discussions that explored the impact of fish consumption on dementia and other health outcomes.

10.6.3 Answering the Research Questions

The aim and objectives of this study explicitly stated in Chapter 2 of this thesis have been accomplished, thereby answering the research questions. The following sections present the summary of how the research questions were answered.

***Research Question 1*:** What are the factors influencing the consumption of fish in older people?

Several factors that could influence the consumption of fish were identified in this study using a quantitative dataset. The sociodemographic factors that could affect and cause lower consumption of fish were identified with older age, female gender, smoking, living in a rural area, having educational level of ≤primary school, occupation of peasant, low income, financial difficulties, being never married/divorced, having undetected hypertension, depression and dementia. However, participants with central obesity and heart disease at baseline had increased odds of fish consumption. Separate data analysis for different levels of fish consumption showed a dose-response trend for these associations. In older Chinese, large socioeconomic inequalities, and certain lifestyle, psychosocial factors and health-related conditions are strong determinants of fish consumption. Such information is important for future development or refinement of effective dietary interventions targeting older adults.

***Research Question 2*:** What is the impact of fish consumption on the incidence of dementia in older people?

This research question was achieved using a quantitative design approach that involves exploring a systematic worldwide literature review, a meta-analysis of available data from the worldwide literature and the Chinese cross-sectional/cohort datasets. Drawing from all these data, the findings reveal a protective effect of fish consumption on the risk of dementia and AD; that is higher consumption of fish is associated with a reduced risk of dementia irrespective of the country's levels of income.

***Research Question 3*:** What is the impact of fish consumption on the prognosis of dementia in older people?

Drawing on the quantitative cohort dataset, this study acknowledged that increased consumption of fish in older people significantly reduce the risk of all-cause mortality with dose-response association. However, no significant association of fish consumption and mortality was found among subgroup of people with dementia. The result shows that fish consumption could not help to prolong life in people already living with dementia. It should be better to increase consumption of fish in the general population to prevent dementia, then increasing the life expectancy in the world.

***Research Question 4*:** What are the perceptions of older people about the impact of fish consumption on dementia?

In the qualitative phase of this study, the findings of the two focus group discussions conducted reveal that participants perceived that fish consumption is beneficial to people's health and can therefore reduce the risk of developing dementia and other health outcomes (e.g. CVD). However, a few of the participants were not completely sure about the beneficial effect of fish consumption.

***Research Question 5*:** What are the views of older people about the determining factors that can affect the consumption of fish?

Two focus group discussions were conducted to complement the results of the quantitative phase of this study and to obtain an in-depth knowledge and understanding about the factors influencing the consumption of fish. Following the factors found in the quantitative phase of this thesis mentioned in research question 1 above, other influencing factors that emerged from the qualitative phase include individual and environmental factors, living in the Mediterranean/coastal areas and childhood/family with children. The individual factors that emerged as enablers of fish consumption include flavour, taste, variety, choice, believe, preference, love/enjoy eating fish, awareness, convenience, education/knowledge, marital status; while difficulty during fish preparation, bony or scaly fish and smell of fish emerged as major individual barriers that could influence the consumption of fish. The environmental factors that could either be an enabler or barrier of fish consumption include availability/accessibility, cost and income.

Therefore, the outcome of this research has highlighted the importance of fish consumption and its possible role in the prevention of dementia, Alzheimer's disease and all-cause mortality and the determinants that could hinder its proper consumption, thereby providing possible strategies required to maintain cognitive health with aging and life expectancy. These results should be extended to improve public health policy, and this could form the basis for further research.

10.6.4 Contribution to Knowledge

The findings of previous systematic review and meta-analyses on the association between fish consumption and the risk of dementia are inconclusive. Those studies are predominantly from the HIC countries, while data from low- and middle-income countries (LMIC) are limited. Few studies have specifically examined the factors influencing the consumption of fish in older people, despite the world population aging. Also, majority of the existing studies on the association of fish consumption with dementia risk employed a quantitative design approach. Therefore, this research makes a substantial contribution to knowledge by utilising a pragmatic mixed methodological approach to answer the research questions. In addition, this research is the first to utilise the Health Belief Model (HBM) in conjunction with Carlucci *et al.* (2015) conceptual framework to explore the impact of fish consumption on the incidence of dementia and all-cause mortality of older people with and without dementia. This study also generated new knowledge about peoples' perception of the association between fish consumption and the risk of dementia, and the determining factors that can affect its consumption.

10.6.5 Conclusion

This current thesis has addressed a major public health problem-the risk of developing dementia-that is becoming more common as the aged population grows. The findings of this thesis improve our understanding about the impact of fish consumption on the incidence of dementia and all-cause mortality in older people with and without dementia. Therefore, it is important to develop strategy to raise public awareness about how the consumption of fish can reduce the risk of dementia and increase life expectancy, since the modification of diet that involve adequate consumption of fish-based diet pose no health risk in addition to other healthy dietary intake and lifestyle. It also offered the opportunity and believes that people can actively get involve in the modification of their diet through adequate consumption of healthy food including fish consumption to improve their cognitive wellbeing throughout the life course. Although, various confounding factors appear to attenuate or moderate the findings, it is very important to be aware of their notable influence and put them into consideration when assessing the effectiveness of fish consumption on the risk of dementia.

In conclusion, since maintaining better cognitive function earlier in life reduces the risk of developing dementia and mortality in later life, it is important to enhance and optimise cognitive function through increasing the consumption of fish in the life course in order to reduce the epidemic of dementia worldwide and to lessen the financial burden affecting the healthcare facility.

REFERENCES

Abraham, C. and Sheeran, P. (2005) 'The Health belief model' in Conner, M. and Norman, P. (editors), *Predicting health behaviour*, Berkshire, England: Open University Press.

Adeniyi, O.R. Omitoyin, S. and Ojo, O. (2012) Socio-economic determinants of consumption pattern of fish among households in Ibadan North Local Government Area of Oyo State, Nigeria. *African Journal of Food, Agriculture, Nutrition and Development*, **12**(5), pp. 6537-6552.

Aglago, E.K. Huybrechts, I. Murphy, N. Casagrande, C. Nicolas, G. Pischon, T. Fedirko, V. Severi, G. Boutron-Ruault, M.C. Fournier, A. and Katzke, V. (2020) Consumption of fish and long-chain n-3 polyunsaturated fatty acids are associated with reduced risk of colorectal cancer in a large European cohort. *Clinical Gastroenterology and Hepatology*, **18**(3), pp.654-666.

Ajzen, I. (1991) The theory of planned behaviour. *Organizational Behaviour and Human decision processes*, **50**, pp. 179-211.

Ajzen, I. and Fishbein, M. (1980) *Understanding attitudes and predicting social behaviour*, Englewood Cliffs, NJ: Prentice-Hall.

Akiyama, H. Barger, S. Barnum, S. Bradt, B. Bauer, J. Cole, G.M. Cooper, N.R. Eikelenboom, P. Emmerling, M. Fiebich, B.L. and Finch, C.E. (2000) Inflammation and Alzheimer's disease. *Neurobiology of aging*, **21**(3), pp.383-421.

Albanese, E. Dangour, A.D. Uauy, R. Acosta, D. Guerra, M. Guerra, S.S.G. Huang, Y. Jacob, K.S. Llibre de Rodriguez, J. Noriega, L.H. and Salas, A. (2009) Dietary fish and meat intake and dementia in Latin America, China, and India: a 10/66 Dementia Research Group population-based study. *The American Journal of Clinical Nutrition*, **90**(2), pp.392-400.

Albanese, E. Lombardo, F.L. Dangour, A.D. Guerra, M. Acosta, D. Huang, Y. Jacob, K.S. Rodriguez, J.D.J.L. Salas, A. Schönborn, C. and Sosa, A.L. (2012) No association between fish intake and depression in over 15,000 older adults from seven low- and middle-income countries–the 10/66 study. *PloS one*, **7**(6), p.e38879.

Altintzoglou, T. Birch Hansen, K. Valsdottir, T. Øyvind Odland, J. Martinsdóttir, E. Brunsø, K. and Luten, J. (2010) Translating barriers into potential improvements: The case of new healthy seafood product development. *Journal of Consumer Marketing*, **27**(3), pp.224-235.

Alzheimer's Association (2016) Alzheimer's disease facts and figures Alzheimer's Association Report. *Alzheimer's & Dementia*, **12**, pp. 459-509.

Amiano, P. Chamosa, S. Etxezarreta, N. Arriola, L. Moreno-Iribas, C. Huerta, J.M. Egües, N. Guevara, M. Navarro, C. Chirlaque, M.D. and Sánchez, M.J. (2016) No association between fish consumption and risk of stroke in the Spanish cohort of the European prospective investigation into Cancer and nutrition (EPIC-Spain): a 13·8-year follow-up study. *Public Health Nutrition*, **19** (4), pp. 674-681.

Amieva, H. Le Goff, M. Millet, X. Orgogozo, J.M. Peres, K. Barberger-Gateau, P. Jacqmin-Gadda, H. and Dartigues, J.F. (2008) Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms. *Annal Neurology,* **64**, pp. 492-498.

Armstrong, R., Hall, B. J., Doyle, J. and Waters, E. (2011) 'Scoping the scope'of a cochrane review. *Journal of public health*, **33**, pp. 147-150.

Andrews, S.J. Marcora, E. and Goate, A. (2019) Causal associations between potentially modifiable risk factors and the Alzheimer's phenome: A Mendelian randomization study. *bioRxiv*, p.689752.

Andel, R. Hughes, T.F. and Crowe, M. (2005) Strategies to reduce the risk for cognitive decline and dementia. *Aging Health*, **1**, pp. 107-116.

Anney, V.N. (2014) Ensuring the quality of the findings of qualitative research: Looking at trustworthiness criteria. *Journal of Emerging Trends in Educational Research and Policy Studies* (JETERAPS), **5**(2), pp.272-281.

Anstey, K. (2014) Optimizing cognitive development over the life course and preventing cognitive decline: Introducing the Cognitive Health Environment Life Course Model (CHELM). *International Journal of Behavioural Development*, **38**(1), pp. 1-10.

Anyanwu, S. (2014) Quantitative analysis of fish consumption in rivers state, Nigeria. *American Journal of Experimental Agriculture*, **4**(4), pp. 469.

Appleton, K.M. Woodside, J.V. Yarnell, J.W. Arveiler, D. Haas, B. Amouyel, P. Montaye, M. Ferrieres, J. Ruidavets, J.B. Ducimetiere, P. Bingham, A. and Evans, A. (2007) Depressed mood and dietary fish intake: direct relationship or indirect relationship as a result of diet and lifestyle? *Journal of affective disorders*, **104**(1-3), pp. 217-223.

Arsil, P. and Yanto, T. (2019) Consumers' Intention and Behaviour towards Fish Consumption: A Conceptual Framework. *In IOP Conference Series: Earth and Environmental Science,* **255**(1), p. 012006.

Arterburn, L.M. Hall, E.B. Oken, H. (2006) Supplement: n–3 Fatty Acids: Recommendations for Therapeutics and Prevention. Distribution, interconversion, and dose response of n–3 fatty acids in humans. *American Journal Clinical Nutrition*, **83**(6), pp. 1467-1476.

Astorg, P. Couthouis, A. Bertrais, S. Arnault, N. Meneton, P. Guesnet, P. Alessandri, J. Galan, P. and Hercberg, S. (2008) Association of fish and long-chain n-3 polyunsaturated fatty acid intakes with the occurrence of depressive episodes in middle-aged French men and women. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, **78**(3), pp. 171-182.

Babbie, E. (1990) *Survey research methods*. Belmont, Calif: Wadsworth Publishing Company.

Bakre, A.T. Chen, R. Khutan, R. Wei, L. Smith, T. Qin, G. Danat, I.M. Zhou, W. Schofield, P. and Clifford, A. (2018) Association between fish consumption and risk of dementia: a new study from China and a systematic literature review and meta-analysis. *Public Health Nutrition*, **21**(10), pp. 1921-1932.

Baltes, P. Staudinger, U. and Lindenberger, U. (1999) Lifespan psychology: Theory and application to intellectual functioning. *Annual Review of Psychology*, **50**, pp. 471-507.

Barberger-Gateau, P. Letenneur, L. Deschamps, V. Pérès, K. Dartigues, J.F. and Renaud, S. (2002) Fish, meat, and risk of dementia: cohort study. *BMJ,* **325**(7370), pp. 932-933.

Barberger-Gateau, P. Jutand, M.A. Letenneur, L. Larrieu, S. Tavernier, B. and Berr, C. (2005) Correlates of regular fish consumption in French elderly community dwellers: data from the Three-City study. *European journal of clinical nutrition*, **59**(7), pp. 817-825.

Barberger-Gateau, P. Raffaitin, C. Letenneur, L. Berr, C. Tzourio, C. Dartigues, J.F. Alperovitch, A. (2007) Dietary patterns and risk of dementia: The Three-City cohort study. *Neurology*, **69**, pp.1921-1930.

Bazan, N.G. (2006) Cell survival matters: docosahexaenoic acid signalling, neuroprotection and photoreceptors. *Trends Neuroscience,* **29**, pp. 263-271.

Barceló-Coblijn, G. and Murphy, E.J. (2009) Alpha-linolenic acid and its conversion to longer chain n− 3 fatty acids: Benefits for human health and a role in maintaining tissue n− 3 fatty acid levels. *Progress in lipid research*, **48**(6), pp. 355-374.

Baumgart, M. Snyder, H.M. Carrillo, M.C. Fazio, S. Kim, H. and Johns, H. (2015) Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimer's & Dementia*, **11**(6), pp.718-726.

Bell, G.A. Kantor, E.D. Lampe, J.W. Kristal, A.R. Heckbert, S.R. and White, E. (2014) Intake of long-chain ω-3 fatty acids from diet and supplements in relation to mortality. *American Journal of Epidemiology*, **179**(6), pp.710-720.

Bellavia, A. Larsson, S.C. and Wolk, A. (2017) Fish consumption and all-cause mortality in a cohort of Swedish men and women. *Journal of Internal Medicine*, **281**(1), pp.86-95.

Beydoun, M.A. Beydoun, H.A. Gamaldo, A.A. Teel, A. Zonderman, A.B. Wang, Y. (2014) Epidemiologic Studies of Modifiable Factors Associated with Cognition and Dementia: Systematic Review and Meta-Analysis. *BMC Public Health*,14, pp. 643.

Birch, D. and Lawley, M.A. (2010) A conceptual framework for investigating fish consumption in Australia. In *Proceedings of ANZMAC*, pp. 1-10.

Birch, D. and Lawley, M. (2012) Buying seafood. Understanding barriers to purchase across consumption segments. *Food Quality and Preference*, **26**(1), pp.12-21.

Birch, D. Lawley, M. and Hamblin, D. (2012) Drivers and barriers to seafood consumption in Australia. *Journal of Consumer Marketing*, **29**(1), pp.64-73.

Birch, D. and Lawley, M. (2014) The role of habit, childhood consumption, familiarity and attitudes across seafood consumption segments in Australia. *Journal of Food Products Marketing*, **20**(1), pp.98-113.

Blacker, R. (2009) A thematic analysis of psychodynamically-oriented supervision of observations in an acute inpatient ward. Published thesis. University of Leicester.

Black, C. N. Bot, M. Scheffer, P. G. Cuijpers, P. and Penninx, B. W. (2015). Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psych neuroendocrinology*, **51**, pp.164-175.

Blok, W.L. Katan, M.B. and van der Meer, J.W. (1996) Modulation of inflammation and cytokine production by dietary (n-3) fatty acids. *The Journal of Nutrition*, **126**(6), pp.1515-1533.

Bourte, J.M. Francois, M. Youyou, A. Dumont, O. Piciotti, M. Pascal, G. (1989) The effects of dietary a-linoleic acid on the composition of nerve membranes, enzymatic activity, amplitude of electrophysiological parameters, resistance to poisons and performance of learning tasks in rats. *Journal Nutrition* **119**, pp.1880-1892.

Bonaccio, M. Ruggiero, E. Di Castelnuovo, A. Costanzo, S. Persichillo, M. De Curtis, A. Cerletti, C. Donati, M.B. de Gaetano, G. Iacoviello, L. and Vermylen, J. (2017) Fish intake is associated with lower cardiovascular risk in a Mediterranean population: Prospective results from the Moli-sani study. *Nutrition, Metabolism and Cardiovascular Diseases*, **27**(10), pp.865-873.

Bowen, G. A. (2008) Naturalistic inquiry and the saturation concept: a research note. *Qualitative research*, **8**(1), pp.137-152.

Boyatzis, R.E. (1998) *Transforming qualitative information: Thematic analysis and code development.* Thousand Oaks, CA: Sage.

Boyce, C. and Neale, P. (2006) *Conducting in-depth interviews: A guide for designing and conducting in-depth interviews for evaluation input*. Watertown, MA: Pathfinder International

Boynton, P.M. and Greenhalgh, T. (2004) Selecting, designing, and developing your questionnaire. *BMJ*, **328**(7451), pp.1312-1315.

Braak, H. Thal, D.R. Ghebremedhin E, Del Tredici, K. (2011) Stages of the pathologic process in Alzheimer disease: Age categories from 1 to 100 years. *Journal Neuropathology Exp Neurology*, **70**, pp. 960-969.

Braman, S.S. (2006) The global burden of asthma. *Chest*, **130**, pp.4-12.

Braun, V. and Clarke, V. (2006) Using thematic analysis in psychology. *Qualitative Research in Psychology*, **3**(2), pp. 77–101.

Bredahl, L. and Grunert, K. G. (1997) Determinants of the consumption of fish and shellfish in Denmark: an application of the theory of planned behavior. In J. B. Luten, T. Børresen, & J. Oehlenschlager (Eds.), Seafood from producer to consumer: Integrated approach to quality (pp. 21–30). Amsterdam: Elsevier.

Brenner, H. Rothenbacher, D. Arndt, V. (2009) Epidemiology of stomach cancer. *Methods Molecular Biology*, **472**, pp.467-477.

Brunsø, K. Verbeke, W. Ottar Olsen, S. and Fruensgaard Jeppesen, L. (2009) Motives, barriers and quality evaluation in fish consumption situations: Exploring and comparing heavy and light users in Spain and Belgium. *British Food Journal*, **111**(7), pp. 699-716.

Bryman, A. (2001) *Social research methods*. Oxford University Press.

Bryman, A. (2006) Barrier to integrating quantitative and qualitative research. *Journal of Mixed Methods Research*, **1**(1), pp. 8-22.

Bryman, A. (2008) *Social research methods*. 3rd Ed. Oxford: Oxford University Press.

Burger, J. and Gochfeld, M. (2009) Perceptions of the risks and benefits of fish consumption. Individual choices to reduce risk and increase health benefits. *Environmental Research*, **109**(3), pp. 343-349.

Calder, P.C. (2004) n–3 Fatty acids and cardiovascular disease: evidence explained, and mechanisms explored. *Clinical science*, **107**(1), pp.1-11.

Calder, P.C. (2006) N-3 Polyunsaturated Fatty Acids, Inflammation, and Inflammatory Diseases. *American Journal Clinical Nutrition*, **83**(6), pp.1505S-1519S.

Calder, P.C. (2013) Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *British Journal Clinical Pharmacology*, **75**(3), pp.645-662.

Carlucci, D. Nocella, G. De Devitiis, B. Viscecchia, R. Bimbo, F. and Nardone, G. (2015) Consumer purchasing behaviour towards fish and seafood products. Patterns and insights from a sample of international studies. *Appetite*, **84**, pp.212-227.

Camic, P. Yardley, L. and Rhodes, J. E. (Eds.). (2003) *Qualitative research in psychology: Expanding perspectives in methodology and design*. Washington, DC: APA Publications.

Can, M.F. Günlü, A. and Can, H.Y. (2015) Fish consumption preferences and factors influencing it. *Food Science and Technology (Campinas)*, **35**(2), pp. 339-346.

Cao, L. Tan, L. Wang, H.F. Jiang, T. Zhu, X.C. Lu, H. Tan, M.S. and Yu, J.T. (2016) Dietary patterns and risk of dementia: a systematic review and meta-analysis of cohort studies. *Molecular neurobiology*, **53**(9), pp. 6144-6154.

Carey, F.G. Lawson, K.D. (1973) Temperature regulation in free swimming blue tuna. *Comparative biochemical ad -physiology A*, **44**(2), pp. 375-392.

Caruana, E.J. Roman, M. Hernández-Sánchez, J. and Solli, P. (2015) Longitudinal studies. *Journal of thoracic disease*, **7**(11), pp. 537-540.

Cederholm, T. Salem Jr, N. and Palmblad, J. (2013) ω-3 fatty acids in the prevention of cognitive decline in humans. *Advances in nutrition*, **4**(6), pp. 672-676.

Chandra, R.K. (2001) Effect of vitamin and trace-element supplementation on cognitive function in elderly subjects. *Nutrition* **17**(9), pp. 709-712.

Chang, C.Y. Ke, D.S. and Chen, J.Y. (2009) Essential fatty acids and human brain. *Acta Neurol Taiwan*, **18**(4), pp. 231-241.

Chapkin, R.S. Davidson, L.A. Ly, L. Weeks, B.R. Lupton, J.R. and McMurray, D.N. (2007) immunomodulatory effects of omega 3 fatty acids putative link to inflammation and colon cancer. *Journal of Nutrition*, **137**(1) pp. 200-204.

Chen, R. Hu, Z. Qin, X. Xu, X. and Copeland, J.R. (2004) A community-based study of depression in older people in Hefei, China—the GMS-AGECAT prevalence, case validation and socio-economic correlates. *International Journal of Geriatric Psychiatry*, **19**(5), pp. 407-413.

Chen, R. Hu, Z. and Seaton, A. (2004) Eating more vegetables might explain reduced asthma symptoms. *BMJ*, **328**(7452), p.1380.

Chen, R. and Tunstall-Pedoe, H. (2005) Socioeconomic deprivation and waist circumference in men and women: The Scottish MONICA surveys 1989–1995. *European Journal Epidemiology* **20**(2), pp.141-147.

Chen, R. Wei, L. Hu, Z. Qin, X. Copeland, J.R. and Hemingway, H. (2005) Depression in older people in rural China. *Archives of Internal Medicine*, **165**(17), pp. 2019-2025.

Chen, R. Hu, Z. Wei, L. Qin, X. McCracken, C. and Copeland, J.R. (2008) Severity of depression and risk for subsequent dementia: cohort studies in China and the UK. *The British Journal of Psychiatry*, **193**(5), pp. 373-377.

Chen, R., Hu, Z., Wei, L., Qin, X. and Copeland, J.R. (2009) Is the relationship between syndromes of depression and dementia temporal? The MRC-ALPHA and Hefei-China studies. *Psychological medicine*, **39**(3), pp.425-430.

Chen, R. (2012) Association of environmental tobacco smoke with dementia and Alzheimer's disease among never smokers. *Alzheimer's & Dementia* **8**(6), pp. 590-595.

Chen, R. Song, Y. Hu, Z. and Brunner, E.J. (2012) Predictors of diabetes in older people in urban China, *PloS one*, **7**(11), pp. e50957.

Chen, R. Ma, Y. Wilson, K. Hu, Z. Sallah, D. Wang, J. Fan, L. Chen, R.L. and Copeland, J.R. (2012) A multicentre community-based study of dementia cases and subcases in older people in China—the GMS-AGECAT prevalence and socio-economic correlates. *International Journal of Geriatric Psychiatry*, **27**(7), pp.692-702.

Chen, R. Zhang, D. Chen, Y. Hu, Z. and Wilson, K. (2012) Passive smoking and risk of cognitive impairment in women who never smoke. *Archives of Internal Medicine*, **172**(3), pp. 271-273.

Chen, R. Hu, Z. Chen, R.L. Ma, Y. Zhang, D. and Wilson, K. (2013) Determinants for undetected dementia and late-life depression. *The British Journal of Psychiatry*, **203**(3), pp.203-208.

Chen, R. Hu, Z. Wei, L. and Wilson, K. (2014) Socioeconomic status and survival among older adults with dementia and depression. *The British Journal of Psychiatry*, **204**(6), pp.436-440.

Chinnathambi, V., Rajasekar, S. and Philominathan, K. (2013) Research Methodology. India: Tamilnada.

Chiu, C.C. Su, K.P. Cheng, T.C. Liu, H.C. Chang, C.J. Dewey, M.E. Stewart, R. and Huang, S.Y. (2008) The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **32**(6), pp.1538-1544.

Christenson, J.K. O'Kane, G.M. Farmery, A.K. and McManus, A. (2017) The barriers and drivers of seafood consumption in Australia: a narrative literature review. *International Journal of Consumer Studies*, **41**(3), pp.299-311.

Cohen, J.T. Bellinger, D.C. Connor, W.E. and Shaywitz, B.A. (2005) A quantitative analysis of prenatal intake of n-3 polyunsaturated fatty acids and cognitive development. *American Journal of Preventive Medicine*, **29**(4), pp.366-366.

Cohen, L. Manion, L. and Morrison, K. (2007) *Research methods in education* 6th edition. London: Routledge.

Cohen, L. Manion, L. and Morrison, K. (2011) *Research methods in education* (7 Ed.). New York, NY: Routledge.

Cole, G.M. Ma, Q.L. and Frautschy, S.A. (2009) Omega-3 fatty acids and dementia. *Prostaglandins, Leukotrienes and Essential fatty acids*, **81**(2-3), pp.213-221.

Cole, G.M. and Frautschy, S.A. (2010) DHA may prevent age-related dementia. *The Journal of nutrition*, **140**(4), pp.869-874.

Collins, P.Y. Patel, V. Joestl, S.S. March, D. Insel, T.R. Daar, A.S. Bordin, I.A. Costello, E.J. Durkin, M. Fairburn, C. and Glass, R.I. (2011) Grand challenges in global mental health. *Nature*, **475**(7354), pp.27-30.

Combs, C.K. Johnson, D.E. Karlo, J.C. Cannady, S.B. Landreth, G.E. (2000) Inflammatory mechanisms in Alzheimer’s disease: inhibition of beta- amyloid stimulated proinflammatory responses and neurotoxicity by PPAR gamma agonists. *Journal Neuroscience*, **20**, pp.558–567.

Connor, W.E. (2000) Importance of n-3 fatty acids in health and disease, *American Journal of Clinical Nutrition*, **71**(1), pp. 171S-175S.

Connor, W.E. and Connor, S.L. (2007) The importance of fish and docosahexaenoic acid in Alzheimer disease. *American Journal Clinical Nutrition*, **85**(4), pp. 929-930.

Cooper, H.M. (2016) *Research Synthesis and Meta-Analysis: A Step-by-Step Approach.* 5th ed. Thousand Oaks, CA: Sage.

Cope, D. (2014) Methods and meanings: credibility and trustworthiness of qualitative research. *Oncology nursing forum.* **41**(1), pp. 89-91.

Copeland, J.R. Prince, M. Wilson, K.C.M. Dewey, M.E. Payne, J. and Gurland, B. (2002) The geriatric mental state examination in the 21st century. *International Journal of Geriatric Psychiatry*, **17**(8), pp.729-732.

Conquer, J.A. Tierney, M.C. Zecevic, J. Bettger, W.J. and Fisher, R.H. (2000) Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. *Lipids*, **35**(12), pp.1305-1312.

Couture, P. Archer, W.R. Lamarche, B. Landry, N. Dériaz, O. Corneau, L. Bergeron, J. and Bergeron, N. (2003) Influences of apolipoprotein E polymorphism on the response of plasma lipids to the ad libitum consumption of a high-carbohydrate diet compared with a high-monounsaturated fatty acid diet. *Metabolism*, **52**(11), pp.1454-1459.

Cole, G.M. Ma, Q.L. and Frautschy, S.A. (2009) Omega-3 fatty acids and dementia. *Prostaglandins, Leukotrienes and Essential fatty acids*, **81**(2-3), pp.213-221.

Collins, P.Y. Patel, V. Joestl, S.S. March, D. Insel, T.R. Daar, A.S. Bordin, I.A. Costello, E.J. Durkin, M. Fairburn, C. and Glass, R.I. (2011) Grand challenges in global mental health. *Nature*, **475**(7354), pp.27-30.

Creswell, J.W. (1994). *Research Design: Qualitative and Quantitative Approaches*, London: SAGE Publications.

Creswell, J.W. (2003) *Research Design: Qualitative, Quantitative and Mixed Methods Approaches* (second edition). Thousand Oaks, CA: Sage Publications.

Creswell, J. W. and Plano Clark, V. L. (2007) *Designing and conducting mixed methods research*. Thousand Oaks, CA: Sage Publications.

Creswell, J. W. (2009) *Research design: qualitative, quantitative, and mixed method approaches*. 3rd Edition. Los Angeles, Calif: Sage Publications.

Creswell, J.W. (2011) *Educational research*. New Delhi: PHI Learning Private Limited.

Creswell, J. (2012) *Qualitative inquiry and research design: Choosing among five approaches* (3rd ed.). Thousand Oaks, CA: Sage.

Creswell, J.W. and Creswell, J.D. (2017) *Research design: Qualitative, quantitative, and mixed methods approaches*. Sage publications.

Creswell, J.W. and Clark, V.L.P. (2017) *Designing and conducting mixed methods research*. Sage publications.

Crotty, M. (1998) *The foundations of social research*. London.: Sage Publications.

Cunnane, S.C. Plourde, M. Pifferi, F. Bégin, M. Féart, C. and Barberger-Gateau, P. (2009) Fish, docosahexaenoic acid and Alzheimer’s disease. *Progress in Lipid Research*, **48**(5), pp.239-256.

Dai, Y. Bai, Y. and Zhang, X. (2017) Fish consumption and prostate cancer risk: a meta-analysis of 37 studies. *International Journal of Clinical and Experimental Medicine*, **10**(7), pp.9891-9900.

Dangour, A.D. Allen, E. Elbourne, D. Fletcher, A. Richards, M. and Uauy, R. (2009) Fish consumption and cognitive function among older people in the UK: baseline data from the OPAL study. *Journal Nutrition Health Aging*, **13**(3), pp. 198–202.

Das, U.N. (2006) Essential fatty acids-a review. *Current pharmaceutical biotechnology*, **7**(6), pp.467-482.

Deary, I.J. Penke, L. and Johnson, W. (2010) The neuroscience of human intelligence differences. *Nature reviews neuroscience*, **11**(3), pp. 201-211.

Denny, A. (2008) An overview of the role of diet during the ageing process *British Journal of Community Nursing*, **13**(2), pp. 58-67.

Denscombe, M. (2008) Communities of practice. *Journal of Mixed Methods Research*, **2**, pp. 270-283.

Denzin, N. K. (2001) *Interpretive interactionism* (Vol. 16). Thousand Oaks, CA.

Denzin, N. K. and Lincoln, Y. S. (2003) *Collecting and interpreting qualitative materials*. Thousand Oaks: Sage Publication.

Denzin, N.K. Lincoln, Y.S. (2005) *Paradigms and perspectives in contention. The Sage handbook of qualitative research*. Thousand Oaks, CA: Sage Publications. pp 183–190.

Devadawson, C. Jayasinghe, C. and Sivakanesan, R. (2015) Socio-demographic factors and fish-eating trends in Eastern community, Sri Lanka, *Journal of Experimental Biology and Agricultural Sciences*, **3**(5), pp. 423-429.

Devore, E.E. Grodstein, F. van Rooij, F.J. Hofman, A. Rosner, B. Stampfer, M.J. Witteman, J.C. and Breteler, M.M. (2009) Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. *American Journal of Clinical Nutrition*, **90**(1), pp.170-176.

Dewey, M.E. Saz P. (2001) Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. *International Journal Geriatrics Psychiatry*, **16**, pp.751-761.

Domingo, J.L. (2007) Omega-3 fatty acids and the benefits of fish consumption: is all that glitters gold? *Environment International*, **33**(7), pp.993-998.

Downes, M.J. Brennan, M.L. Williams, H.C. and Dean, R.S. (2016) Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open* **6**(12), pp. e011458-2016-011458.

Egger, M. Smith, G.D. Schneider, M. and Minder, C. (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**(7109), pp. 629-634.

Engelhart, M.J. Geerlings, M.I. Ruitenberg, A. Van Swieten, J.C. Hofman, A. Witteman, J.C.M. and Breteler, M.M.B. (2002) Diet and risk of dementia: Does fat matter? The Rotterdam Study. *Neurology*, **59**(12), pp. 1915-1921.

Engeset, D. Braaten, T. Teucher, B. Kühn, T. Bueno-de-Mesquita, H.B. Leenders, M. Agudo, A. Bergmann, M.M. Valanou, E. Naska, A. and Trichopoulou, A. (2015) Fish consumption and mortality in the European Prospective Investigation into Cancer and Nutrition cohort. *European Journal of Epidemiology*, **30**(1), pp.57-70.

Eilander, A. Hundscheid, D. Osendarp, S.J. Transler, C. and Zock, P.L. (2007) Effects of n-3 long chain polyunsaturated fatty acid supplementation on visual and cognitive development throughout childhood: a review of human studies. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **76**(4), pp.189-203.

Elwood, M. (2007) *Critical Appraisal of Epidemiological Studies and Clinical Trials*. 3rd Ed Oxford University Press; Oxford: pp. 1-570.

Erdogan, B.E. Mol, S. and Cosansu, S. (2011) Factors influencing the consumption of seafood in Istanbul, Turkey. *Turkish Journal of Fisheries and Aquatic Sciences*, **11**(4), pp. 631-639.

Etikan, I. Musa, S.A. and Alkassim, R.S. (2016) Comparison of convenience sampling and purposive sampling. *American Journal of theoretical and applied statistics*, **5**(1), pp.1-4.

Evans, B.C. Coon, D.W. and Ume, E. (2011) Use of theoretical frameworks as a pragmatic guide for mixed methods studies: A methodological necessity? Journal of mixed methods research, **5**(4), pp. 276-292.

Feilzer, M.Y. (2010) Doing Mixed Methods Research Pragmatically: Implications for the Rediscovery of Pragmatism as a Research Paradigm. *Journal of Mixed Methods Research*, **4**(1), pp. 6-16.

Ferlay, J. Soerjomataram, I. Ervik, M. Dikshit, R. Eser, S. Mathers, C. Rebelo, M. Parkin, D.M. Forman, D. Bray, F. (2013) GLOBOCAN 2012 v1.0 cancer incidence and mortality worldwide: IARC Cancer Base No. 11. 2013. Available at: http://globocan.iarc.fr, (accessed on December10, 2018).

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. (2015) Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal Cancer*, **136**, pp. E359–E386.

Ferlay, J. Colombet, M. Soerjomataram, I. Mathers, C. Parkin, D.M. Piñeros, M. Znaor, A. and Bray, F. (2019) Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *International Journal of Cancer*, **144**(8), pp.1941-1953.

Fetters, M.D. Curry, L.A. and Creswell, J.W. (2013) Achieving integration in mixed methods designs—principles and practices. *Health services research*, **48**(6pt2), pp. 2134-2156.

Fischer, K. Melo van Lent, D. Wolfsgruber, S. Weinhold, L. Kleineidam, L. Bickel, H. Scherer, M. Eisele, M. van den Bussche, H. Wiese, B. and König, H.H. (2018) Prospective Associations between Single Foods, Alzheimer's Dementia and Memory Decline in the Elderly. *Nutrients*, **10**(7), pp.852.

Fishbein, M. and Ajzen, I. (1975). *Belief, attitude, intention and behaviour: An introduction to theory and research*. Reading, MA: Addison-Wesley.

Foltyn, P. (2015) Ageing, dementia and oral health. *Australian Dental Journal*, **60**(1), pp. 86-94

Food and Agricultural Organisation of the United Nations (FAO) (2016) The State of World Fisheries and Aquaculture: Contributing to Food Security and Nutrition for All: In Brief. Available at: http://www.fao.org/3/a-i5555e.pdf (accessed 10th September 2016).

Food and Agricultural Organisation of the United Nations (FAO) (2018) The State of World Fisheries and Aquaculture: Meeting the Sustainable Development Goals. Available at: http://www.fao.org/3/i9540en/i9540en.pdf (accessed 25th October 2018).

Fotuhi, M. Mohassel, P. and Yaffe, K. (2009) Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer's disease: a complex association. *Nature Reviews Neurology*, **5**(3), pp.140.

Frambach, J.M. van der Vleuten, C.P. and Durning, S.J. (2013) AM last page: Quality criteria in qualitative and quantitative research. *Academic Medicine*, **88**(4), p.552.

Fratiglioni, L. Launer, L.J. Andersen, K. Breteler, M.M. Copeland, J.R. Dartigues, J.F. Lobo, A. Martinez-Lage, J. Soininen, H. and Hofman, A. (2000) Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology*, **54**(11 Suppl 5), pp.10-15.

Galobardes, B. Morabia, A. and Bernstein, M.S. (2001) Diet and socioeconomic position: does the use of different indicators matter? *International Journal of Epidemiology*, **30**(2), pp. 334-340.

Gamoh, S. Hashimoto, M. Sugioka, K. Hossain, M.S. Hata, N. Misawa, Y. and Masumura, S. (1999) Chronic administration of docosahexaenoic acid improves reference memory-related learning ability in young rats. *Neuroscience*, **93**(1), pp.237-241.

Ganguli, M. Dodge, H.H. Shen, C. Pandav, R.S. and DeKosky, S.T. (2005) Alzheimer disease and mortality: a 15-year epidemiological study. *Archives of Neurology*, **62**(5), pp.779-784.

Gao, C. M. Ding, J.H. Li, S.P. et al (2014). Meat, fish and egg intake and risk of breast cancer. *Asian Pacific Journal Cancer Prevention*, **15**, pp. 7879-7884.

Gartside, D. and Kirkegaard, I. (2010) A history of fishing. Interactions: *Food, Agriculture and Environment*, **2**, pp.70-80.

Gazi, I. Liberopoulos, E.N. Saougos, V.G. and Elisaf, M. (2006) Beneficial effects of omega-3 fatty acids: the current evidence. *Hellenic Journal Cardiology*, **47**(4), pp.223-231.

Geelen, A. Schouten, J.M. Kamphuis, C. Stam, B.E. Burema, J. Renkema, J.M. Bakker, E.J. van't Veer, P. and Kampman, E. (2007) Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. *American Journal of Epidemiology*, **166**(10), pp.1116-1125.

Gil, A. (2002) Polyunsaturated fatty acids and inflammatory diseases. *Biomedical Pharmacotherapy*, **56**, pp.388-396.

Gil, A. and Gil, F. (2015) Fish, a Mediterranean source of n-3 PUFA: benefits do not justify limiting consumption. *British Journal of Nutrition*, **113**(S2), pp. S58-S67.

Gillum, S. (1991) Understanding the uptake of cervical cancer screening: the contribution of Health Belief Model, *British Journal of General Practice,* **41**, pp. 510-513.

Gillum, R.F. Mussolino, M. and Madans, J.H. (2000) The relation between fish consumption, death from all causes, and incidence of coronary heart disease: the NHANES I Epidemiologic Follow-up Study. *Journal of Clinical Epidemiology*, **53**(3), pp.237-244.

Glanz, K. Rimer, B.K. and Viswanath, K. eds., (2015) *Health behavior and Health education: Theory, research, and practice*. John Wiley & Sons.

Glesne, C. (2010) *Becoming qualitative researchers*: An introduction (4th ed.). Boston, MA: Pearson.

Golafshani, N. (2003) Understanding reliability and validity in qualitative research. *The qualitative report*, **8**(4), pp.597-606.

Goldman, K.J. (1997) Regulation of body temperature in the white shark, carcharodo carcharia. *Journal of comparative physiology Biochemical systemic and environmental physiology* **167(**6), pp. 423-442.

Gorard, G. (2004) *Combining methods in educational and social research*. Berkshire: Open

University Press.

Gould, J.F. Smithers, L.G. Makrides, M. (2013) The effect of maternal omega-3 (n-3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. *American Journal Clinical Nutrition*, **97**(3), pp.531-544.

Grant, W.B. (2003) Diet and risk of dementia: does fat matter? The Rotterdam Study. *Neurology* **60**(12), pp.2020-2021.

Grieger, J.A. Miller, M. and Cobiac, L. (2012) Knowledge and barriers relating to fish consumption in older Australians. *Appetite,* **59**(2), pp.456-463.

Grix, J. (2002) Introducing students to the generic terminology of social research. *Politics*, **22**(3), pp.175-186.

Grosso, G. Micek, A. Marventano, S. Castellano, S. Mistretta, A. Pajak, A. and Galvano, F. (2016) Dietary n-3 PUFA, fish consumption and depression: A systematic review and meta-analysis of observational studies. *Journal of Affective Disorders*, **205**, pp.269-281.

Guehne, U. Riedel-Heller, S. and Angermeyer, M.C. (2005) Mortality in dementia. *Neuroepidemiology*, **25**(3), pp.153-162.

Haag, M. (2003) Essential fatty acids and the brain. *The Canadian Journal of Psychiatry*, **48**(3), pp.195-203.

Hashimoto, M. Tanabe, Y. Fujii, Y. Kikuta, T. Shibata, H. and Shido, O. (2005) Chronic administration of docosahexaenoic acid ameliorates the impairment of spatial cognition learning ability in amyloid β–infused rats. *Journal of Nutrition*, **135**(3), pp.549-555.

Hay, C. (2006) *Political ontology*. The Oxford handbook of contextual political analysis, pp.78-96.

He, J. Vupputuri, S. Allen, K. Prerost, M.R. Hughes, J. and Whelton, P.K. (1999) Passive smoking and the risk of coronary heart disease—a meta-analysis of epidemiologic studies. *New England Journal of Medicine*, **340**(12), pp. 920-926.

He, K. Rimm, E.B. Merchant, A. Rosner, B.A. Stampfer, M.J. Willett, W.C. and Ascherio, A. (2002) Fish consumption and risk of stroke in men. *Jama*, **288**(24), pp.3130-3136.

He, K. Song, Y. Daviglus, M.L. Liu, K., Van Horn, L. Dyer, A.R. and Greenland, P. (2004a) Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation,* **109**(22), pp. 2705-2711.

He, K. Song, Y. Daviglus, M.L. Liu, K. Van Horn, L., Dyer, A.R. Goldbourt, U. and Greenland, P. (2004b) Fish consumption and incidence of stroke: a meta-analysis of cohort studies, *Stroke; Journal of cerebral circulation*, **35**(7), pp. 1538-1542.

He, K. (2009) Fish, long-chain omega-3 polyunsaturated fatty acids and prevention of cardiovascular disease-eat fish or take fish oil supplement? *Progress Cardiovascular Diseases,* **52**, pp. 95-114.

Hengeveld, L.M. Praagman, J. Beulens, J.W.J. Brouwer, I.A. van der Schouw, Y.T. and Sluijs, I. (2018) Fish consumption and risk of stroke, coronary heart disease, and cardiovascular mortality in a Dutch population with low fish intake. *European Journal of Clinical Nutrition*, **72**(7), pp.942-950.

Henwood, K. (2014) Qualitative research. *Encyclopedia of Critical Psychology*, pp.1611-1614.

Heppner, F.L. Ransohoff, R.M. and Becher, B. (2015) Immune attack: the role of inflammation in Alzheimer disease. *Nature Reviews Neuroscience,* **16**(6), pp.358-372.

Hesse-Biber, S. (2015) Mixed methods research: The "thing-ness" problem. *Qualitative health research*, **25**(6), pp. 775-788.

Hicks, D. Pivarnik, L. and McDermott, R. (2008) Consumer perceptions about seafood–an internet survey, *Journal of Foodservice*, **19**(4), pp. 213-226.

Higgins, J.P. Thompson, S.G. Deeks, J.J. and Altman, D.G. (2003) Measuring inconsistency in meta-analyses. *BMJ*, **327**(7414), pp.557-560.

Higuchi, A. Davalos, J. and Hernani-Merino, M. (2017) Theory of planned behaviour applied to fish consumption in modern Metropolitan Lima. *Food Science and Technology*, **37**(2), pp.202-208.

Hill, A.B. (1965) The Environment and Disease: Association or Causation? Proceeding Royal Society Medicine **58**, pp. 295-300.

Hoepfl, M. C. (1997) Choosing qualitative research: A primer for technology education researchers. *Journal of Technology Education*, **9**(1), 47-63.

Horrocks, L.A. Yeo, Y.K. (1999) Health benefits of docosahexaenoic acid (DHA). *Pharmacology Research*, **40**, pp. 211-225.

Horrocks, L.A. and Farooqui, A.A. (2004) Docosahexaenoic acid in the diet: its importance in maintenance and restoration of neural membrane function. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, **70**(4), pp.361-372.

Howe, K. R. (1988) Against the quantitative-qualitative incompatibility thesis or dogmas die hard. *Educational researcher*, **17**(8), pp. 10-16.

Huang, T.L. Zandi, P.P. Tucker, K.L. Fitzpatrick, A.L. Kuller, L.H. Fried, L.P. Burke, G.L. and Carlson, M.C. (2005) Benefits of fatty fish on dementia risk are stronger for those without APOE ε4. *Neurology*, **65**(9), pp.1409-1414.

Huang, T.L. (2010) Omega-3 fatty acids, cognitive decline, and Alzheimer's disease: a critical review and evaluation of the literature. *Journal Alzheimer's Disease,* **21**(3), pp. 673-690.

Hulley, S.B. Cummings, S.R. Browner, W.S. et al. (2001) *Designing Clinical Research: An Epidemiologic Approach*. 2nd Ed Lippincott Williams & Wilkins; Philadelphia: pp. 1-336.

Humphris, G. and Ling M.S. (2000) *Behavioural sciences for dentistry*, London: Churchill Livingstone.

Hu, F.B. Wilett, W.C. (2002) Optimal diets for prevention of coronary heart disease. *JAMA*, **288**, pp. 2569-2578.

Huxley, R. Mendis, S. Zheleznyakov, E. Reddy, S. and Chan, J. (2010) Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk—a review of the literature. *European Journal of Clinical Nutrition*, **64**(1), pp.16-22.

Innis, S.M. (2007) Dietary (n-3) fatty acids and brain development. *Journal Nutrition*, **137**(4), pp. 855-859.

Ioannidis, J.P. Patsopoulos, N.A. and Evangelou, E. (2007) Uncertainty in heterogeneity estimates in meta-analyses. *BMJ*, **335**(7626), pp. 914-916.

Iriyama, S. Nakahara, S. Jimba, M. Ichikawa, M. and Wakai, S. (2007) AIDS health beliefs and intention for sexual abstinence among male adolescent students in Kathmandu, Nepal: A test of perceived severity and susceptibility. *Public health*, **121**(1), pp.64-72.

Iso, H. Rexrode, K.M. Stampfer, M.J. Manson, J.E. Colditz, G.A. Speizer, F.E. Hennekens, C.H. and Willett, W.C. (2001) Intake of fish and omega-3 fatty acids and risk of stroke in women. *Jama*, **285**(3), pp.304-312.

Jack Jr, C.R. Knopman, D.S. Jagust, W.J. Shaw, L.M. Aisen, P.S. Weiner, M.W. Petersen, R.C. and Trojanowski, J.Q. (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurology*, **9**(1), pp. 119-128.

Jack Jr, C.R. Knopman, D.S. Jagust, W.J. Petersen, R.C. Weiner, M.W. Aisen, P.S. Shaw, L.M. Vemuri, P. Wiste, H.J. Weigand, S.D. and Lesnick, T.G. (2013) Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurology*, **12**(2), pp.207-216.

Jacka, F.N. Pasco, J.A. Williams, L.J. Meyer, B.J. Digger, R. and Berk, M. (2013) Dietary intake of fish and PUFA, and clinical depressive and anxiety disorders in women. *British Journal of nutrition*, **109**(11), pp.2059-2066.

Jaeger, S.R. and Meiselman, H.L. (2004) Perceptions of meal convenience: The case of at-home evening meals, *Appetite*, **42**(3), pp. 317-325.

James, M.J. Gibson, R.A. Cleland, L.G. (2000) Dietary polyunsaturated fatty acids and inflammatory mediator production. *American Journal Clinical Nutrition,* **71**, pp. 343-348.

James, B.D. Leurgans, S.E. Hebert, L.E., Scherr, P.A., Yaffe, K. and Bennett, D.A. (2014) Contribution of Alzheimer disease to mortality in the united states. *Neurology*, **82**, pp.1045-1050.

Janz, N.K. and Becker, M. (1984) The Health Belief Model: A decade Later. *Health Education* **11**(1), pp. 1-47.

Jarrett, N. C. Adeyemi, S. A. and Huggins, T. (2006) Bridging the gap: providing healthcare to newly released men. *Journal of Healthcare for the Poor and Underserved,* **17**(1), pp. 70-80.

Jayedi, A. Shab-Bidar, S. Eimeri, S. and Djafarian, K. (2018) Fish consumption and risk of all-cause and cardiovascular mortality: a dose–response meta-analysis of prospective observational studies. *Public Health Nutrition,* **21**(7), pp.1297-1306.

Jayedi, A. and Shab-Bidar, S. (2020) Fish Consumption and the Risk of Chronic Disease: An Umbrella Review of Meta-Analyses of Prospective Cohort Studies. *Advances in Nutrition*. 11(5), pp.1123-1133.

Jensen, H.H. (2006) Changes in seafood consumer preference patterns and associated changes in risk exposure. *Marine pollution bulletin*, **53**(10), pp. 591-598.

Jiang, T. Yu, J.T. Tian, Y. and Tan, L. (2013) Epidemiology and etiology of Alzheimer's disease: from genetic to non-genetic factors. *Current Alzheimer Research*, **10**(8), pp. 852-867.

Jimoh, K.A. and Mohammed, S.T. (2015) Analysis of fish demand in Ilorin-West Local Government Area, Kwara State, Nigeria. *International Journal of Agriculture, Forestry and Fisheries*, **3**, pp.148-154.

Johansson, L. Solvoll, K. Bjørneboe, G.A. and Drevon, C. (1998) Intake of very-long-chain n-3 fatty acids related to social status and lifestyle. *European journal of clinical nutrition*, **52**(10), pp. 716.

Johnson, B. and Turner, L.A. (2003): Data collection strategies in mixed methods research. In

Tashakkori, A. and Teddlie, C. editors, Handbook of mixed methods in social and behavioral sciences. Sage, 297-319.

Johnson, R. B. and Onwuegbuzie, A. J. (2004) Mixed methods research: A research paradigm whose time has come. *Educational researcher*, **33**(7), pp.14-26.

Johnson, R. B. Onwuegbuzie, A. J. and Turner, L. A. (2007) Toward a definition of mixed methods research. *Journal of Mixed Methods Research*, **1**(2), pp. 112-133.

Jaeger, S.R. and Meiselman, H.L. (2004) Perceptions of meal convenience: The case of at-home evening meals, *Appetite*, **42**(3), pp. 317-325.

Juhl, H. J. Poulsen, C.S. (2000) Antecedents and effects of consumer involvement in fish as a product group. *Appetite*, **34**(3), pp. 261-267.

Jump, D.B. (2002) Dietary polyunsaturated fatty acids and regulation of gene transcription. *Current Opinion Lipidology*, **13**, pp.155-164.

Kalmijn, S. Launer, L.J. Ott, A. Witteman, J.C. Hofman, A. and Breteler, M.M. (1997) Dietary fat intake and the risk of incident dementia in the Rotterdam Study. *Annals of neurology*, **42**(5), pp.776-782.

Kalmijn, S. van Boxtel, M.P. Ocke, M. Verschuren, W.M. Kromhout, D. and Launer, L.J. (2004) Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology*, **62**(2), pp. 275-280.

Karmali, R.A. (1989) n-3 Fatty acids and cancer. *Journal International Medicine*, **225**, pp.197-200.

Kawarazuka, N. (2010) The contribution of fish intake, aquaculture, and small-scale fisheries to improving nutrition: A literature review: The World Fish Centre Working Paper. Available: http://www.worldfishcenter.org/resource_centre/WF_2590.pdf (accessed 1st March 2018).

Kelle, (2006) Combining qualitative and quantitative methods in research practice: purposes and advantages. *Qualitative Research in Psychology*, **3**, pp. 293-311.

Kesse-Guyot, E. Peneau, S. Ferry, M. Jeandel, C. Hercberg, S. Galan, P. and SU. VI. Max 2 Research Group, (2011) Thirteen-year prospective study between fish consumption, long-chain n-3 fatty acids intakes and cognitive function. *The Journal of Nutrition, Health and Aging*, **15**(2), pp.115-120.

Kim, M. Nam, J.H. Oh, D.H. and Park, Y. (2010) Erythrocyte α-linolenic acid is associated with the risk for mild dementia in Korean elderly. *Nutrition Research*, **30**(11), pp. 756-761.

Kim, D.H. Grodstein, F. Rosner, B. Kang, J.H. Cook, N.R. Manson, J.E. Buring, J.E. Willett, W.C. and Okereke, O.I. (2013) Seafood types and age-related cognitive decline in the Women's Health Study. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, **68**(10), pp.1255-1262.

Kim, E.K. and Ju, S.Y. (2019) Asthma and Dietary Intake of Fish, Seaweeds, and Fatty Acids in Korean Adults. *Nutrients*, **11**(9), p.2187-2199.

Kiyabu, G.Y. Inoue, M. Saito, E. Abe, S.K. Sawada, N. Ishihara, J. Iwasaki, M. Yamaji, T. Shimazu, T. Sasazuki, S. and Shibuya, K. (2015) Fish, n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids intake and breast cancer risk: The Japan Public Health Center-based prospective study. *International Journal of Cancer*, **137**(12), pp.2915-2926.

Kitzinger, J. (1995) Qualitative research: Introducing focus groups. *British Medical Journal*, **311**, pp. 299-302.

Ko, G.T. Tang, J. Chan, J.C. Sung, R. Wu, M.M. Wai, H.P. and Chen, R. (2001) Lower BMI cut-off value to define obesity in Hong Kong Chinese: an analysis based on body fat assessment by bioelectrical impedance. *British Journal of Nutrition*, **85**(2), pp.239-242.

Kotani, S. Sakaguchi, E. Warashina, S. Matsukawa, N. Ishikura, Y. Kiso, Y. Sakakibara, M. Yoshimoto, T. Guo, J. and Yamashima, T. (2006) Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. *Neuroscience research*, **56**(2), pp.159-164.

Kotwal, S. Jun, M. Sullivan, D. Perkovic, V. and Neal, B. (2012) Omega 3 fatty acids and cardiovascular outcomes: systematic review and meta-analysis. *Circulation: Cardiovascular Quality and Outcomes*, **5**(6), pp.808-818.

Kreider, C.R. Gempesaw, C.M. Bacon, J.R. Toensmeyer, U.C. and Groff, A.J. (1993) An Analysis of Consumer Perceptions of Fresh Fish and Seafood in the Delmarva Region. *Journal of Food Distribution Research*, **4**, pp. 37-48.

Krueger, R.A. (1998) *Developing Questions for Focus Groups*, Thousand Oaks, California: Sage Publications.

Krueger, R.A. and Casey, M.A. (2000) *Focus Groups: A Practical Guide for Applied Research*, 3rd ed. Thousand Oaks, California: Sage Publications.

Krueger, R.A. Casey, M.A. (2009) *Focus groups, a practical guide for applied research*. 4th ed. Thousand Oaks, CA: Sage Publications.

Krueger, R.A. and Casey, M.A. (2014) *Focus groups: A practical guide for applied research*. Sage publications.

Kwak, S.M. Myung, S.K. Lee, Y.J. Seo, H.G. and Korean Meta-analysis Study Group (2012) Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Archives of Internal Medicine*, **172**(9), pp.686–694.

Larrieu, S. Letenneur, L. Berr, C. Dartigues, J. Ritchie, K. Alperovitch, A. Tavernier, B. and Barberger-Gateau, P. (2004a) Sociodemographic Differences in Dietary Habits in a Population-Based Sample of Elderly Subjects: The 3C Study. *Journal of Nutrition, Health & Aging*, **8**(6), pp. 497-502.

Larrieu, S. Letenneur, L. Helmer, C. Dartigues, J.F. and Barberger-Gateau, P. (2004b) Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. *Journal of Nutrition, Health & Aging*, **8**(3), pp.150-154.

Larsson, S.C. and Orsini, N. (2011) Fish consumption and the risk of stroke: a dose-response meta-analysis. *Stroke*, **42**(12), pp. 3621-3623.

Lee, L.K. Shahar, S. Chin, A.V. and Yusoff, N.A.M. (2013) Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. *Psychopharmacology*, **225**(3), pp.605-612.

Leek, S. Maddock, S. and Foxall, G. (2000) Situational determinants of fish consumption. *British food journal*, **102**(1), pp.18-39.

Li, H. Houston, J.E. Wang, S. and Lee, H. (2001) Factors affecting consumer preferences for fish in Taiwan, International Institute of Fisheries Economics and Trade (IIFET) 2000 Proceedings, pp. 1-7.

Li, J. Xun, P. Zamora, D. Sood, A. Liu, K. Daviglus, M. Iribarren, C. Jacobs Jr, D. Shikany, J.M. and He, K. (2012) Intakes of long-chain omega-3 (n− 3) PUFAs and fish in relation to incidence of asthma among American young adults: the CARDIA study–. *The American Journal of Clinical Nutrition*, **97**(1), pp.173-178.

Li, F. Liu, X. Zhang, D. (2016) Fish consumption and risk of depression: a meta-analysis. *Journal Epidemiology Community Health*, **70**(3), pp. 299-304.

Li, N. Wu, X. Zhuang, W. Xia, L. Chen, Y. Wu, C., Rao, Z. Du, L. Zhao, R. Yi, M. and Wan, Q. (2020) Fish consumption and multiple health outcomes: Umbrella review. *Trends in Food Science & Technology*, **99**(2020), pp.273-283.

Liberati, A. Altman, D.G. Tetzlaff, J. Mulrow, C. Gøtzsche, P.C. Ioannidis, J.P. Clarke, M. Devereaux, P.J. Kleijnen, J. Moher, D. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine*, **6**, p.e1000100.

Lincoln, Y. S. and Guba, E. G. (1985) *Naturalistic inquiry*. Newbury Park, CA: Sage.

Lingard, L. Albert, M. Levinson, W. (2008) Qualitative Research Grounded Theory: mixed methods and action research. *BMJ*, **337**, pp. 459-461.

Lobo, A. Launer, L.J. Fratiglioni, L. Andersen, K. Di Carlo, A. Breteler, M.M.B. Copeland, J.R.M. Dartigues, J.F. Jagger, C. Martinez-Lage, J. and Soininen, H. (2000) Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. *Neurology*, **54**(5), p.S4.

Lopez, L. Kritz-Silverstein, D. Barrett-Connor, E. (2011) High dietary and plasma levels of the omega-3 fatty acid docosahexaenoic acid are associated with decreased dementia risk: the Rancho Bernardo study. *Journal of Nutrition Health Aging* **15**(1), pp. 25-31.

López-Campos, J.L. Tan, W. and Soriano, J.B. (2016) Global burden of COPD. *Respirology*, **21**(1), pp.14-23.

Lucas, M. Mirzaei, F. O'Reilly, E.J. Pan, A. Willett, W.C. Kawachi, I. Koenen, K. and Ascherio, A. (2011) Dietary intake of n− 3 and n− 6 fatty acids and the risk of clinical depression in women: a 10-y prospective follow-up study. *The American journal of clinical nutrition*, **93**(6), pp.1337-1343.

Luchtman, D.W. and Song, C. (2013) Cognitive enhancement by omega-3 fatty acids from childhood to old age: findings from animal and clinical studies. *Neuropharmacology*, **64**, pp. 550-565.

Lund, E.K. (2013) Health benefits of seafood; is it just the fatty acids? *Food Chemistry*, **140** (3), pp. 413-420.

Mackenzie, N. and Knipe, S. (2006) Research dilemmas: Paradigms, methods and methodology. *Issues in educational research*, **16**(2), pp.193-205.

Mack, L. (2010) The philosophical underpinnings of educational research. 5-11.

Mahon, D. Cowan, C. and McCarthy, M. (2006) The role of attitudes, subjective norm, perceived control and habit in the consumption of ready meals and takeaways in Great Britain, *Food Quality and Preference*, **17**(6), pp. 474-481.

Mann, J.I. Appleby, P.N. Key, T.J. and Thorogood, M. (1997) Dietary determinants of ischaemic heart disease in health-conscious individuals. *Heart*, **78**(5), pp.450-455.

Martin, B. (2017) *What are Fish?* Encyclopaedia Britannica. Newyork: Britannica Educational Publishing.

Mathers, N. Fox, N. and Hunn, A. (2007) Surveys and questionnaires. *Trent: RDSU.*

Matsuoka, Y.J. Sawada, N. Mimura, M. Shikimoto, R. Nozaki, S. Hamazaki, K. Uchitomi, Y. and Tsugane, S. (2017) Dietary fish, n-3 polyunsaturated fatty acid consumption, and depression risk in Japan: a population-based prospective cohort study. *Translational psychiatry*, **7**(9), pp.1242-1248.

Maxwell, J. (2005) Qualitative Research Design: An Interactive Approach. 2nd edition. Thousand Oaks, CA: Sage.

May, N. and Pope, C. (2000) Qualitative research in health care: assessing quality in qualitative research. *British Medical Journal*, **320**(7226), p.50.

McKeever, T.M. Bitton, J. (2004) Diet and asthma. *American Journal Respiratory Critical Care Medicine*, **170**, pp. 725-729.

McManus, A. Burns, S.K. Howat, P.A. Cooper, L. Fielder, L. (2007) Factors influencing the consumption of sea food among young children in Perth: a qualitative study. *BCM Public Health*, **7**(1), pp. 119-127.

McManus, A. Hunt, W. Howieson, J. Cuesta-Briand, B. McManus, J. and Storey, J. (2012) Attitudes towards seafood and patterns of consumption in an Australian coastal town. *Nutrition Bulletin*, **37**(3), pp. 224-231.

McMillan, J. and Schumacher, S. (2006) *Research in Education*. (6th ed.) Boston: Pearson Education.

Mertens, D.M. (2005) *Research methods in education and psychology: Integrating diversity with quantitative and qualitative approaches*. (2nd ed.) Thousand Oaks: Sage.

Mischoulon, D. and Freeman, M.P. (2013) Omega-3 fatty acids in psychiatry. *Psychiatric Clinics*, **36**(1), pp.15-23.

Mohanty, B.P. Ganguly, S. Mahanty, A. Sankar, T.V. Anandan, R. Chakraborty, K. Paul, B.N. Sarma, D. Syama Dayal, J. Venkateshwarlu, G. and Mathew, S. (2016) DHA and EPA content and fatty acid profile of 39 food fishes from India. *BioMed research international*, pp 1-14.

Moher, D. Liberati, A. Tetzlaff, J. and Altman, D.G. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine*, **151**(4), pp.264-269.

Moher, D. Shamseer, L. Clarke, M. Ghersi, D. Liberati, A. Petticrew, M. Shekelle, P. and Stewart, L.A. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*, **4**(1), pp.1-9.

Morabia, A. (2004) A History of Epidemiologic Methods and Concepts. Birkhaeuser Verlag; Basel: pp. 1-405.

Mori, T.A. (2017) Marine Omega-3 fatty acids in the prevention of cardiovascular disease. *Fitoterapia*, **123**, pp. 51-58.

Morgan, D.L. Scannell, A.U. (1998) *Planning Focus Groups*. Thousand Oaks, California: Sage Publications.

Morris, M.C. Evans, D.A. Bienias, J.L. Tangney, C.C. Bennett, D.A. Wilson, R.S. Aggarwal, N. and Schneider, J. (2003) Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurology*, **60**(7), pp. 940-946.

Morris, M.C. Evans, D.A. Tangney, C.C. Bienias, J.L. and Wilson, R.S. (2005) Fish consumption and cognitive decline with age in a large community study. *Archives Neurology*, **62**(12), pp. 1849-1853.

Morris, M.C. (2016) Nutrition and risk of dementia: overview and methodological issues. *Annals of the New York Academy of Sciences*, **1367**(1), pp.31-37.

Morrison and Lykestos (2005) Pathophysiology of AD. Adv stud Nur, **3**(8) pp. 256-270

Moses, J. Dwana, D. Giroh, D. Jimjel, Z. Oluwaseun, A. (2015) The influence of socio-economic characteristics on consumers' preference on fish purchase in Yola North Local Government Area, Adamawa State. International Journal of Environmental & Agriculture Research, **1**, pp.1-11.

Mozaffarian, D. Lemaitre, R.N. Kuller, L.H. Burke, G.L. Tracy, R.P. and Siscovick, D.S. (2003) Cardiac benefits of fish consumption may depend on the type of fish meal consumed: The Cardiovascular Health Study. *Circulation*, **107**(10), pp.1372-1377.

Myrland, O. Trondsen, T. Johnston, R.S. and Lund, E. (2000) Determinants of seafood consumption in Norway. Lifestyle, revealed preferences, and barriers to consumption. *Food Quality and Preference*, **11**(3), pp. 169-188.

Nagel, G. and Linseisen, J. (2005) Dietary intake of fatty acids, antioxidants and selected food groups and asthma in adults. *European Journal of Clinical Nutrition*, **59**(1), p.8.

Nakamura, Y. Ueshima, H. Okamura, T. Kadowaki, T. Hayakawa, T. Kita, Y. Tamaki, S. Okayama, A. and NIPPON DATA80 Research Group (2005) Association between fish consumption and all-cause and cause-specific mortality in Japan: NIPPON DATA80, 1980–99. *The American Journal of Medicine*, **118**(3), pp.239-245.

Namazi, N. Brett, N.R. Bellissimo, N. Larijani, B. Heshmati, J. and Azadbakht, L. (2019) The association between types of seafood intake and the risk of type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. *Health promotion perspectives*, **9**(3), pp.164-173.

Natacci, L. M. Marchioni, D. C. Goulart, A. Nunes, M.A. B. Moreno, A. O. Cardoso, L. Giatti, L. B. Molina, M. S. Santos, I. R. Brunoni, A. and Lotufo, A. P. (2018) Omega 3 Consumption and Anxiety Disorders: A Cross-Sectional Analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Nutrients*, **10**(6), p.663.

Naumann, F. A. Gempesaw, C. M. Bacon, J. R. and Manalo, A. (1995) Consumer choice for fresh fish: Factors affecting purchase decisions. *Marine Resource Economics*, **10**, pp. 117-142.

Neale, E. P. Nolan-Clark, D. Probst, Y. C. Batterham, M. J. and Tapsell, L. C. (2012) Comparing attitudes to fish consumption between clinical trial participants and non-trial individuals. *Nutrition and Dietetics*, **69**(2), pp.124-129.

Nestel, P.J. (2000) Fish oil and cardiovascular disease: lipids and arterial function. *American Journal Clinical Nutrition*, **71**(1), pp. 228S-231S.

Newman, A.B. Fitzpatrick, A.L. Lopez, O. Jackson, S. Lyketsos, C. Jagust, W. Ives, D. DeKosky, S.T. and Kuller, L.H. (2005) Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *Journal of the American Geriatrics Society*, **53**(7), pp.1101-1107.

Ngabirano, L. Samieri, C. Feart, C. Gabelle, A. Artero, S. Duflos, C. Berr, C. and Mura, T. (2019) Intake of Meat, Fish, Fruits, and Vegetables and Long-Term Risk of Dementia and Alzheimer's Disease. *Journal of Alzheimer's Disease*, **68** (2019), pp.711-722.

Nindrea, R.D. Aryandono, T. Lazuardi, L. and Dwiprahasto, I. (2019) Protective Effect of Omega-3 Fatty Acids in Fish Consumption Against Breast Cancer in Asian Patients: A Meta-Analysis. *Asian Pacific journal of cancer prevention: APJCP*, **20**(2), pp.327-332.

Nooyens, A.C. Van Gelder, B.M. Bueno-de-Mesquita, H.B. Van Boxtel, M.P. and Verschuren, W.M. (2018) Fish consumption, intake of fats and cognitive decline at middle and older age: the Doetinchem Cohort Study. *European Journal of Nutrition*, **57**(4), pp.1667-1675.

Ogawa, S. (2014) Nutritional management of older adults with cognitive decline and dementia. *Geriatrics & gerontology international*, **14**, pp.17-22.

Okada, M. Amamoto, T. Tomonaga, M. Kawachi, A. Yazawa, K. Mine, K. and Fujiwara, M. (1996) The chronic administration of docosahexaenoic acid reduces the spatial cognitive deficit following transient forebrain ischemia in rats. *Neuroscience*, **71**(1), pp.17-25.

O'Leary, Z. (2004) *The essential guide to doing research*. London: Sage.

Oomen, C.M. Feskens, E.J. Räsänen, L. Fidanza, F. Nissinen, A.M. Menotti, A. Kok, F.J. and Kromhout, D. (2000) Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. *American Journal of Epidemiology*, **151**(10), pp.999-1006.

Onwuegbuzie, A. and Frels, R. (2016) *Seven steps to a comprehensive literature review*. Los Angeles: Sage.

Olsen, S. O. (2001) Consumer involvement in seafood as family meals in Norway. An application of the expectancy-value approach. *Appetite*, **36**(2), pp.173-186.

Olsen, S. O. (2003) Understanding the relationship between age and seafood consumption. The mediating role of attitude, health involvement and convenience. *Food Quality and Preference*, **14**(3), pp.199-209.

Olsen, S.O. (2004) Antecedents of Seafood Consumption Behaviour - An Overview. *Journal of Aquatic Food Product Technology*, **13**(3), pp. 79-91.

Osler, M. Andreasen, A.H. and Hoidrup, S. (2003) No inverse association between fish consumption and risk of death from all-causes, and incidence of coronary heart disease in middle-aged, Danish adults. *Journal of clinical epidemiology*, **56**(3), pp.274-279.

Otsuka, R. Tange, C. Nishita, Y. Tomida, M. Kato, Y. Imai, T. Ando, F. and Shimokata, H. (2019) Fish and Meat Intake, Serum Eicosapentaenoic Acid and Docosahexaenoic Acid Levels, and Mortality in Community-Dwelling Japanese Older Persons. *International Journal of Environmental Research and Public health*, **16**(10), p.1806.

Outzen, M. Tjønneland, A. Christensen, J. and Olsen, A. (2018) Fish consumption and prostate cancer risk and mortality in a Danish cohort study. *European Journal of Cancer Prevention*, **27**(4), pp.355-360.

Owens, C.S. Crone, D. Gidlow, C. and James, D.V. (2018) Observational (cross-sectional and longitudinal) studies. *Research Methods in Physical Activity and Health*, p.74.

Parkin, D.M. Bray, F. Ferlay, J. and Pisani, P. (2005) Global cancer statistics, 2002. *CA: A Cancer Journal for Clinicians*, **55**(2), pp.74-108.

Patton, M. Q. (2002) *Qualitative evaluation and research methods* (3rd ed.). Thousand Oaks, CA: Sage Publications, Inc.

Pieniak, Z. Verbeke, W. and Scholderer, J. (2010) Health-related beliefs and consumer knowledge as determinants of fish consumption. *Journal of Human Nutrition and Dietetics*, **23**(5), pp.480–488.

Polit, D.F. and Beck, C.T. (2008) *Nursing research: Generating and assessing evidence for nursing practice*. 8th Edition Philadelphia, PA: Lippincott Williams and Wilkins.

Polit, D. F. and Beck, C. T. (2010) *Essentials of nursing research: appraising evidence for nursing practice.* 7th Ed. Philadelphia: Lippincott Williams & Wilkins.

Polit, D. F. and Beck, C. T. (2012) *Nursing research: Principles and methods* (9th ed). Baltimore: Lippincott Williams and Wilkins.

Poss, J.E. (2001) Developing a new model for cross-cultural research: synthesizing the health belief model and the theory of reasoned action. *Advances in Nursing Science*, **23**(4), pp.1-15.

Prince, M. Acosta, D. Chiu, H. Scazufca, M. Varghese, M. and 10/66 Dementia Research Group (2003) Dementia diagnosis in developing countries: a cross-cultural validation study. *The Lancet* **361**(9361), pp. 909-917.

Prince, M. Acosta, D. Chiu, H. Copeland, J. Dewey, M. Scazufca, M. and 10/66 Dementia Research Group. (2004) Effects of education and culture on the validity of the Geriatric Mental State and its AGECAT algorithm. *The British Journal of Psychiatry*, **185**(5), pp. 429-436.

Prince, M.J. De Rodriguez, J.L. Noriega, L. Lopez, A. Acosta, D. Albanese, E. Arizaga, R. Copeland, J.R. Dewey, M. Ferri, C.P. and Guerra, M. (2008) The 10/66 Dementia Research Group's fully operationalised DSM-IV dementia computerized diagnostic algorithm, compared with the 10/66 dementia algorithm and a clinician diagnosis: a population validation study. *BMC public health*, **8**(1), p.219.

Prince, M. Albanese, E. Guerchet M. and Prina, M. (2014) Nutrition and Dementia: a review of available research. https://www.alz.co.uk/sites/default/files/pdfs/nutrition-and-dementia.pdf (accessed 20 August 2016).

Prince, M. Wimo, A. Guerchet, M. Ali, G.C. Wu, Y.T. Prina, M. (2015) The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends. http://www.alz.co.uk/research/worldreport- 2015 (accessed 15 August 2016).

Qin, B. Plassman, B.L. Edwards, L.J. Popkin, B.M. Adair, L.S. and Mendez, M.A. (2014) Fish intake is associated with slower cognitive decline in Chinese older adults. *The Journal of nutrition*, **144**(10), pp.1579-1585.

Qiu, C. X. De Ronchi, D. and Fratiglioni, L. (2007) The epidemiology of the dementias: an update. *Current opinion in psychiatry*, **20**(4), pp.380-385.

Qiu, C. Kivipelto, M. and von Strauss, E. (2009) Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues in clinical neuroscience*, **11**(2), pp.111-128.

Raatz, S.K. Silverstein, J.T. Jahns, L. and Picklo, M.J. (2013) Issues of fish consumption for cardiovascular disease risk reduction. Nutrients, **5**(4), pp.1081-1097.

Raskin, J. Cummings, J. Hardy, J. Schuh, K. Dean, R.A. (2015) Neurobiology of Alzheimer's disease: Integrated molecular, physiological, anatomical, biomarker, and cognitive dimensions. *Current Alzheimer Research* **12**, pp. 712-722.

Reitz, C. Brayne, C. and Mayeux, R. (2011) Epidemiology of Alzheimer disease. *Nature Reviews Neurology*, **7**(3), p.137.

Rhee, J.J. Kim, E. Buring, J.E. and Kurth, T. (2017) Fish consumption, omega-3 fatty acids, and risk of cardiovascular disease. *American Journal of Preventive Medicine*, **52**(1), pp.10-19.

Rizos, E.C. Ntzani, E.E. Bika, E. Kostapanos, M.S. Elisaf, M.S. (2012) Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*, **308**(10), pp. 1024–1033.

Rizos, E.C. Elisaf, M.S. (2013) Current evidence and future perspectives of omega-3polyunsaturated fatty acids for the prevention of cardiovascular disease. *European Journal of Pharmacology*, **706** (1-3) pp.1-3.

Robson, C. (2011) *Real world research* (3rd ed.). Chichester, UK: Wiley.

Rodriguez, J.J.L. Ferri, C.P. Acosta, D. Guerra, M. Huang, Y. Jacob, K.S. Krishnamoorthy, E.S. Salas, A. Sosa, A.L. Acosta, I. and Dewey, M.E. (2008) Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. *The Lancet*, **372**(9637), pp.464-474.

Roer-Strier, D. and Kurman, J. (2009) Combining qualitative and quantitative methods to study perceptions of immigrant youth. *Journal of Cross-Cultural Psychology,* **40**(6), pp. 988-995.

Rortveit, A. W. and Olsen, S. O. (2009) Combining the role of convenience and consideration set size in explaining fish consumption in Norway. *Appetite*, **52**(2), pp.313-317.

Roman, G.C. Jackson, R.E. Gadhia, R. Roman, A.N. and Reis, J. (2019) Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. *Revue neurologique*, **175**(10), pp.724-741.

Ronald, A. (2006). The cross-sectional study: Investigating Prevalence and Association Department of Health Studies and Statistics. The University of Chicago.

Rose, D.P. Connolly, J.M. (1999) Omega-3 fatty acids as cancer chemo preventive agents. *Pharmacology Therapy,* **83**, pp.217-244.

Rosenstock, I. M., Stretcher, V. J. and Becker, M. H. (1988) Social Learning theory and the health belief model, *Health Education Quarterly,* **15**, pp.175-183.

Ruxton, C. H. S. Reed, S. C. Simpson, M. J. A. and Millington, K. J. (2004) The health benefits of omega-3 polyunsaturated fatty acids: a review of the evidence. *Journal Human Nutrition Dietetic*, **17**, pp. 449-459.

Ryan, A.S. Astwood, J.D. Gautier, S. Kuratko, C.N. Nelson, E.B. and Salem, Jr, N. (2010) Effects of long-chain polyunsaturated fatty acid supplementation on neurodevelopment in childhood: a review of human studies. *Prostaglandins, Leukotrienes and Essential Fatty Acids* (PLEFA), **82**(4-6), pp.305-314.

Sahrhage, D. and Lundbeck, J. (1992) Early Times. In: A History of Fishing. Springer, Berlin, Heidelberg pp. 5-55.

Sale, J.E. Lohfeld, L.H. and Brazil, K. (2002) Revisiting the quantitative-qualitative debate: Implications for mixed-methods research. *Quality and quantity*, **36**(1), pp.43-53.

Salem, N. Jr, Litman, B, Kim, H.Y, Gawrisch, K. (2001) Mechanisms of action of docosahexaenoic acid in the nervous system. *Lipids*, **36**(9), pp. 945-959.

Sallis, J.F. Cervero, R.B, Ascher, W. Henderson, K.A. Kraft, M.K. Kerr, J. (2006) An ecological approach to creating active living communities. *Annual Review Public Health*, **27**, pp.297-322.

Samieri, C. Morris, M.C. Bennett, D.A. Berr, C., Amouyel, P. Dartigues, J.F. Tzourio, C. Chasman, D.I. and Grodstein, F. (2018) Fish intake, genetic predisposition to Alzheimer disease, and decline in global cognition and memory in 5 cohorts of older persons. *American Journal of Epidemiology*, **187**(5), pp.933-940.

Sanchez-Villegas, A. Henríquez, P. Figueiras, A. Ortuño, F. Lahortiga, F. Martínez-González, M.A. (2007) Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study. *European Journal Nutrition*, **46**, pp.337-346.

Sánchez-Villegas, A. Álvarez-Pérez, J. Toledo, E. Salas-Salvadó, J. Ortega-Azorín, C. Zomeño, M., Vioque, J. Martínez, J. Romaguera, D. Pérez-López, J. and López-Miranda, J. (2018) Seafood Consumption, Omega-3 Fatty Acids Intake, and Life-Time Prevalence of Depression in the PREDIMED-Plus Trial. Nutrients, **10**(12), p.2000.

Sauvaget, C. Nagano, J. Allen, N. Grant, E.J. and Beral, V. (2003) Intake of animal products and stroke mortality in the Hiroshima/Nagasaki Life Span Study. *International Journal of Epidemiology*, **32**(4), pp.536-543.

Schaefer, E.J. Bongard, V. Beiser, A.S. Lamon-Fava, S. Robins, S.J. Au, R. Tucker, K.L. Kyle, D.J. Wilson, P.W. and Wolf, P.A. (2006) Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. *Archive of Neurology* **63**(11), pp.1545-1550.

Schaie, K.W. (2005) *Developmental Influences on Adult Intelligence: The Seattle Longitudinal Study*. New York: Oxford University Press.

Schiepers, O. De Groot, R. Jolles, J. and Van Boxtel, M. (2010) Fish consumption, not fatty acid status, is related to quality of life in a healthy population. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, **83** (1), pp. 31-35.

Scholderer, J. and Grunert, K. G. (2001) Does generic advertising work? A systematic evaluation of the Danish campaign for fresh fish. Aquaculture Economics and Management, **5**, pp.253-271.

Sedgwick, P. (2014) Cross sectional studies: advantages and disadvantages. *BMJ*, **348**, pp. 2276-2277.

Seo, T. Blaner, W.S. Deckelbaum, R.J. (2005) Omega-3 fatty acids: molecular approaches to optimal biological outcomes. *Current Opinion Lipidology*, **16**, pp. 11-18.

Shahar, E. Folsom, A.R. Melnick, S.L. Tockman, M.S. Comstock, G.W. Gennaro, V. Higgins, M.W. Sorlie, P.D. Ko, W.J. and Szklo, M. (1994) Dietary n-3 polyunsaturated fatty acids and smoking-related chronic obstructive pulmonary disease. *New England Journal of Medicine*, **331**(4), pp.228-233.

Sharifan, P. Hosseini, M.S. and Sharifan, A. (2017) The interventional relationship between frequent fish consumption and depression symptoms in aging adults: A randomized controlled trial. *International Journal of Geriatric Psychiatry*, **32**(12), pp. 116-122.

Siddaway, A. P. Wood, A. M. and Hedges, L. V. (2019) How to do a systematic review: a best practice guide for conducting and reporting narrative reviews, meta-analyses, and meta-syntheses. *Annual review of psychology*, **70**, pp. 747-770.

Sidhu, K.S. (2003) Health benefits and potential risks related to consumption of fish or fish oil. *Regulatory Toxicology and Pharmacology*, **38**, pp. 336-344.

Singh, M. (2005) Essential fatty acids, DHA and human brain. *Indian Journal Pediatric*, **72**, pp.239-242.

Smit, H.A. Grievink, L. and Tabak, C. (1999) Dietary influences on chronic obstructive lung disease and asthma: a review of the epidemiological evidence. *Proceedings of the Nutrition Society*, **58**(2), pp.309-319.

Smith, B. Sparkes, A.C. Phoenix, C. and Kirkby1, J. (2012) Qualitative research in physical therapy: a critical discussion on mixed-method research. *Physical Therapy Reviews*,**17**(6), pp. 374-381.

Somekh, B. and Lewin, C. (2005) *Research methods in social sciences*. London: Sage.

Solfrizzi, V. Custodero, C. Lozupone, M. Imbimbo, B.P. Valiani, V. Agosti, P., Schilardi, A. D'Introno, A. La Montagna, M. Calvani, M. and Guerra, V. (2017) Relationships of dietary patterns, foods, and micro-and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. *Journal of Alzheimer's Disease*, **59**(3), pp.815-849.

Song, J.W. and Chung, K.C. (2010) Observational studies: cohort and case-control studies. *Plastic and reconstructive surgery*, **126** (6), p.2234.

Song, J. Su, H. Wang, B.L. Zhou, Y.Y. and Guo, L.L. (2014) Fish consumption and lung cancer risk: systematic review and meta-analysis. *Nutrition and Cancer*, **66**(4), pp.539-549.

Stalmeijer, R.E. McNaughton, N. and Van Mook, W.N. (2014) Using focus groups in medical education research: AMEE Guide No. 91. *Medical teacher*, **36**(11), pp. 923-939.

Stern, Y. (2009) Cognitive reserve. *Neuropsychologia*, **47**, pp. 2015-2028.

Stern, Y. (2012) Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, **11**, pp. 1006-1012.

Stewart, D.W. and Shamdasani, P.N. (2014) *Focus groups: Theory and practice* (Vol. 20). Sage publications.

Strauss, A. and Corbin, J. (1990) *Basics of qualitative research: Grounded theory procedures and techniques*. Newbury Park, CA: Sage Publications, Inc.

Strudwick, A. and Morris, R. (2010) A qualitative study exploring the experiences of African-Caribbean informal stroke carers in the UK. *Clinical Rehabilitation*, **24**, pp. 159-167.

Subedi, D. (2016) Explanatory sequential mixed method design as the third research community of knowledge claim. *American Journal of Educational Research*, **4**(7), pp.570-577.

Sukamolson, S. (2007) Fundamentals of quantitative research. Language Institute Chulalongkorn University, pp.1-20.

Szymanski, K.M. Wheeler, D.C. and Mucci, L.A. (2010) Fish consumption and prostate cancer risk: a review and meta-analysis. *The American journal of clinical nutrition*, **92**(5), pp.1223-1233.

Takata, Y. Zhang, X. Li, H. Gao, Y.T. Yang, G. Gao, J. Cai, H. Xiang, Y.B. Zheng, W. and Shu, X.O. (2013) Fish intake and risks of total and cause-specific mortality in 2 population-based cohort studies of 134,296 men and women. *American journal of epidemiology*, **178**(1), pp.46-57.

Tanskanen, A. Hibbeln, J.R. Tuomilehto, J. Uutela, A. Haukkala, A. Viinamäki, H. Lehtonen, J. and Vartiainen, E. (2001) Fish consumption and depressive symptoms in the general population in Finland. *Psychiatric Services*, **52**(4), pp. 529-531.

Tariq, S. and Woodman, J. (2010) Using mixed methods in health research. *Journal of the Royal Society of Medicine Short Reports*, **0**, p. 1-8.

Tashakkori, A. and Teddlie, C. (Eds.) (2003) *Handbook of mixed methods in social and behavioral research*. Thousand Oaks, CA: Sage.

Tashakkori, A. and Teddlie, C. eds., (2010) Sage handbook of mixed methods in social & behavioral research. Sage.

Taylor, R. Najafi, F. Dobson, A. (2007) Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. *International Journal Epidemiology*, **36**(5), pp.1048-1059.

Thomas, L. MacMillan, J. McColl, E. Hale, C. and Bond, S. (1995) Comparison of focus group and individual interview methodology in examining patient satisfaction with nursing care. *Social Sciences in Health*, **1**, pp. 206-219.

Thong, N.T. and Solgaard, H.S. (2017) Consumer's food motives and seafood consumption. *Food Quality and Preference*, **56**, pp.181-188.

Thorgilsson, B. Nunes, M.L. and Gunnlaugsdóttir, H. (2010) Review of evidence for the beneficial effect of fish consumption. Available at: https://www.matis.is/media/matis/utgafa/51-10-beneficial-effect-of-fish-consumption-QALIBRA.pdf (accessed 10th August 2017) (internet).

Thorsdottir, F. Sveinsdottir, K. Jonsson, F. H. Einarsdottir, G. Thorsdottir, I. and Martinsdottir, E. (2012) A model of fish consumption among young consumers. *Journal of Consumer Marketing*, **29**(1), pp. 4-12.

Tidwell, J.H. and Allan, G.L. (2001) Fish as food: aquaculture's contribution: Ecological and economic impacts and contributions of fish farming and capture fisheries. *EMBO reports*, **2**(11), pp. 958-963.

Troisi, R.J. Willett, W.C. Weiss, S.T. Trichopoulos, D. Rosner, B. and Speizer, F.E. (1995) A prospective study of diet and adult-onset asthma. *American Journal of Respiratory and Critical Care Medicine*, **151**(5), pp.1401-1408.

Trondsen, T. Scholderer, J. Lund, E., and Eggen, A. E. (2003) Perceived barriers to consumption of fish among Norwegian women. *Appetite*, **41**(3), pp. 301-314.

Trondsen, T. Braaten, T. Lund, E. and Eggen, A. (2004) Health and seafood consumption patterns among women aged 45–69 years. A Norwegian seafood consumption study. *Food Quality and Preference*, **15**(2), pp. 117-128.

Tsukada, H. Kakiuchi, T. Fukumoto, D. Nishiyama, S. and Koga, K. (2000) Docosahexaenoic acid (DHA) improves the age-related impairment of the coupling mechanism between neuronal activation and functional cerebral blood flow response: a PET study in conscious monkeys. *Brain Research*, **862**(1-2), pp.180-186.

Tsurumaki, N. Zhang, S. Tomata, Y. Abe, S. Sugawara, Y. Matsuyama, S. and Tsuji, I. (2019) Fish consumption and risk of incident dementia in elderly Japanese: The Ohsaki Cohort 2006 Study. *British Journal of Nutrition*, **122**(10), pp.1182-1191.

Tully, A.M. Roche, H.M. Doyle, R. Fallon, C. Bruce, I. Lawlor, B. Coakley, D. and Gibney, M.J. (2003) Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case–control study. *British Journal of Nutrition*, **89**(4), pp. 483-489.

Uauy, R. and Dangour, A.D. (2006) Nutrition in brain development and aging: role of essential fatty acids. *Nutrition Reviews*, **64**(2), pp. S24-S33.

Upadhyay, A. Pandey, D. Singh, Y.J. (2014) Socio-Economic Determinants of Consumption Pattern of Fish in Urban Area of Tripura. *Economic Affairs*, **59**(3), pp. 355-362.

van Gelder, B.M. Tijhuis, M. Kalmijn, S. Kromhout, D. (2007) Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *American Journal of Clinical Nutrition*, **85**(4), pp. 1142-1147.

van de Rest, O. Spiro III, A. Krall-Kaye, E. Geleijnse, J.M. de Groot, L.C. and Tucker, K.L. (2009) Intakes of (n-3) fatty acids and fatty fish are not associated with cognitive performance and 6-year cognitive change in men participating in the Veterans Affairs Normative Aging Study. *Journal of Nutrition*, **139**(12), pp.2329-2336.

Van De Vorst, I.E. Vaartjes, I. Geerlings, M.I. Bots, M.L. and Koek, H.L. (2015) Prognosis of patients with dementia: results from a prospective nationwide registry linkage study in the Netherlands. *BMJ open*, **5**(10), p.e008897.

Varraso, R. Barr, R.G. Willett, W.C. Speizer, F.E. and Camargo Jr, C.A. (2014) Fish intake and risk of chronic obstructive pulmonary disease in 2 large US cohorts–. *The American Journal of Clinical Nutrition*, **101**(2), pp.354-361.

Verbeke, W. and Vackier, I. (2005) Individual determinants of fish consumption: application of the theory of planned behavior. *Appetite*, **44**(1), pp. 67-82.

Verbeke, W. (2006) Functional foods: consumer willingness to compromise on taste for health? *Food Quality and Preference*, **17**(1/2), pp. 126-131.

Verbeke, W. Vanhonacker, F. Frewer, L. J. Sioen, I. De Henauw, S. and Van Camp, J. (2008) Communicating risks and benefits from fish consumption. Impact on Belgian consumers' perception and intention to eat fish. *Risk Analysis*, **28**(4), pp. 951-967.

Villegas, R. Takata, Y. Murff, H. and Blot, W.J. (2015) Fish, omega-3 long-chain fatty acids, and all-cause mortality in a low-income US population: results from the Southern Community Cohort Study. *Nutrition, Metabolism and Cardiovascular Diseases*, **25**(7), pp.651-658.

Wagner, M. Dartigues, J.F. Samieri, C. Proust-Lima, C. (2018) Modeling risk-factor trajectories when measurement tools change sequentially during follow-up in cohort studies: Application to dietary habits in prodromal dementia. *American Journal Epidemiology,* **187**, pp. 845-854.

Wainwright, P.E. (2002) Dietary essential fatty acids and brain function: a developmental perspective on mechanisms. *Proceedings of the Nutrition Society*, **61**(1), pp. 61-69.

Wallin, A. Di Giuseppe, D. Orsini, N. Patel, P.S. Forouhi, N.G. and Wolk, A. (2012) Fish consumption, dietary long-chain n-3 fatty acids, and risk of type 2 diabetes: systematic review and meta-analysis of prospective studies. *Diabetes care*, **35**(4), pp.918-929.

Wang, M.P. Thomas, G.N. Ho, S.Y. Lai, H.K. Mak, K.H. and Lam, T.H. (2011) Fish consumption and mortality in Hong Kong Chinese—the LIMOR study. *Annals of epidemiology*, **21**(3), pp.164-169.

Wang, Q. Liang, X. Wang, L. Lu, X. Huang, J. Cao, J. Li, H. and Gu, D. (2012) Effect of omega-3 fatty acids supplementation on endothelial function: a meta-analysis of randomized controlled trials. *Atherosclerosis*, **221**(2), pp.536-543.

Wan, Y. Zheng, J. Wang, F. and Li, D. (2017) Fish, long chain omega-3 polyunsaturated fatty acids consumption, and risk of all-cause mortality: a systematic review and dose-response meta-analysis from 23 independent prospective cohort studies. *Asia Pacific Journal of Clinical Nutrition*, **26**(5), p.939.

Ward, R.E. Cho, K. Quaden, R.M. Nguyen, X.M.T. Ho, Y.L. Vassy, J. Gagnon, D.R. Wilson, P. Gaziano, J.M. Djousse, L. and VA Million Veteran Program, (2018) Fish Consumption is Not Associated with the Risk of Coronary Heart Disease or Stroke. *Circulation*, **137**(1), pp. AP218-AP218.

Weichselbaum, E. Coe, S. Buttriss, J. and Stanner, S. (2013) Fish in the diet: A review. *Nutrition Bulletin*, **38**(2), pp.128-177.

Wells, G. Shea, B. O'Connell, D. Robertson, J. Peterson, J. Welch, V. Losos, M. and Tugwell, P. (2014) The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/nos_manual.pdf (accessed 17 August 2016).

Wenaty, A. Mabiki, F. Chove, B. and Mdegela, R. (2018) Fish consumers preferences, quantities of fish consumed and factors affecting fish eating habits: A case of Lake Victoria in Tanzania. *International Journal of Fisheries and Aquatic Studies*; **6**(6), pp.247-252.

Weuve, J. Hebert, L.E. Scherr, P.A. and Evans, D.A. (2014) Deaths in the United States among persons with Alzheimer's disease (2010–2050). *Alzheimer's & Dementia*, **10**(2), pp. 40-46.

Whalley, L. J. Dick, F. D. and McNeill, G. (2006) A life–course approach to the aetiology of late–onset dementias. *The Lancet Neurology*, **5**, pp. 87-96.

Whelton, J. He, P.K. Whelton, P. Muntner, (2004) Meta-analysis of observational studies on fish intake and coronary heart disease. *American Journal Cardiology*, **93**(9), pp. 1119-1123.

Wilkinson, S. (2004) Focus groups: A feminist method. In S.N. Hesse-Biber & M.L. Yaiser (eds.), Feminist perspectives on social research (pp. 271–295). New York: Oxford University Press.

Wilson, K.C.M., Taylor, S., Copeland, J.R.M., Chen, R. and McCracken, C.F.M. (1999) Socio-economic deprivation and the prevalence and prediction of depression in older community residents. *The British Journal of Psychiatry*, **175**(6), pp.549-553.

Wimo, A. Ljunggren, G. Winblad, B. (1997) Costs of dementia and dementia care: a review. *International Journal Geriatrics Psychiatry*, **12**, pp.841-856.

Wittchen, H.U. Jacobi, F. Rehm, J. Gustavsson, A. Svensson, M. Jönsson, B. Olesen, J. Allgulander, C. Alonso, J. Faravelli, C.L.F.P.J. and Fratiglioni, L. (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European neuropsychopharmacology*, **21**(9), pp.655-679.

World Health Organisation (2011) Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation, Geneva, 8-11 December 2008. Available at: https://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf;jses (accessed 10th August 2018) (internet).

World Health Organisation (2011) Global status report on non-communicable diseases 2010. Available at: https://apps.who.int/iris/bitstream/handle/10665/44579/9789240686458_eng.pdf (accessed 12th June 2018) (internet).

World Health Organisation (2014) Global status report on noncommunicable diseases 2014. Available at: https://apps.who.int/iris/bitstream/handle/10665/148114/9789241564854_eng.pdf. (accessed 10th August 2018) (internet).

World Health Organisation (2015) Epidemiology and impact of dementia: Current State and Future Trends. Available at: http://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf. (accessed 15th October 2017) (internet).

World Health Organisation (2018) The top 10 causes of death fact sheets. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. (accessed 21st October 2018) (internet).

World Health Organisation (2019) Dementia fact sheets. Available at: http://www.who.int/mediacentre/factsheets/fs362/en/. (accessed 20th September 2019) (internet).

Wolverhampton Profile Information and Statistics, (2014), *Mid-Year Population Estimates*. Available at: http://www.wolverhamptoninprofile.org.uk/ (accessed 31st March 2020) (internet).

Wu, S. Liang, J. Zhang, L. Zhu, X. Liu, X. and Miao, D. (2011) Fish consumption and the risk of gastric cancer: systematic review and meta-analysis. *BMC cancer*, **11**(1), pp.26-35.

Wu, S. Feng, B. Li, K. Zhu, X. Liang, S. Liu, X. Han, S. Wang, B. Wu, K. Miao, D. and Liang, J. (2012a) Fish consumption and colorectal cancer risk in humans: a systematic review and meta-analysis. *The American Journal of Medicine*, **125**(6), pp.551-559.

Wu, J.H. Micha, R. Imamura, F. Pan, A. Biggs, M.L. Ajaz, O. Djousse, L. Hu, F.B. and Mozaffarian, D. (2012b) Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. *British Journal of Nutrition*, **107**(S2), pp. S214-S227.

Wu, S. Ding, Y. Wu, F. Li, R. Hou, J. and Mao, P. (2015) Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: A meta-analysis. *Neuroscience & Biobehavioral Reviews*, **48**, pp.1-9.

Wu, Y.T. Teale, J. Matthews, F.E. Brayne, C. Woods, B. Clare, L. and Ageing Study Wales research team (2016) Lifestyle factors, cognitive reserve, and cognitive function: results from the Cognitive Function and Ageing Study Wales, a population-based cohort. *The Lancet*, **388**, p.S114.

Xiao, Y. and Li, X. (1999) Polyunsaturated fatty acids modify mouse hippocampal neuronal excitability during excitotoxic or convulsant stimulation. *Brain Research*, **846**(1), pp. 112-121.

Xun, P. and He, K. (2012) Fish consumption and incidence of diabetes: meta-analysis of data from 438,000 individuals in 12 independent prospective cohorts with an average 11-year follow-up. *Diabetes care*, **35**(4), pp.930-938.

Xu, M. Fang, Y.J. Chen, Y.M. Lu, M.S. Pan, Z.Z. Yan, B. Zhong, X. and Zhang, C.X. (2015) Higher freshwater fish and sea fish intake is inversely associated with colorectal cancer risk among Chinese population: a case-control study. *Scientific reports*, **5**, p.12976.

Yaktine, A.L. and Nesheim, M.C. (2007) Seafood choices: balancing benefits and risks, National Academies Press.

Yamagishi, K. Iso, H. Date, C. Fukui, M. Wakai, K. Kikuchi, S. Inaba, Y. Tanabe, N. and Tamakoshi, A. and JACC Study Group (2008) Fish, ω-3 Polyunsaturated Fatty Acids, and Mortality from Cardiovascular Diseases in a Nationwide Community-Based Cohort of Japanese Men and Women: The JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. *Journal of the American College of Cardiology*, **52**(12), pp. 988-996.

Yang, H. Xun, P. He, K. (2013) Fish and fish oil intake in relation to risk of asthma: a systematic review and meta-analysis. *PloS one*, **8**(11), pp. e80048.

Yang, Y. and Je, Y. (2018a) Fish consumption and depression in Korean adults: the Korea National Health and Nutrition Examination Survey, 2013–2015. *European journal of clinical nutrition*, **72**(8), p.1142.

Yang, Y. Kim, Y. and Je, Y. (2018b) Fish consumption and risk of depression: Epidemiological evidence from prospective studies. *Asia-Pacific Psychiatry*, **10**(4), p.e12335.

Yehuda, S. Raiovitz, S. Arasso, R.L. Mostofsky, D.L. (2002) The role of polyunsaturated fatty acid in restoring the aging neuronal membrane. *Neurology Aging*, **23**, pp. 843-853.

Young, G. and Conquer, J. (2005) Omega-3 fatty acids and neuropsychiatric disorders. *Reproduction, nutrition, development*, **45**, pp. 1-28.

Yuan, J.M. Ross, R.K. Gao, Y.T. and Yu, M.C. (2001) Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *American Journal of Epidemiology*, **154**(9), pp.809-816.

Yu, X.F. Zou, J. and Dong, J. (2014) Fish consumption and risk of gastrointestinal cancers: a meta-analysis of cohort studies. *World Journal of Gastroenterology: WJG*, **20**(41), p.15398.

Zeng, L.F. Cao, Y. Liang, W.X. Bao, W.H. Pan, J.K. Wang, Q. Liu, J. Liang, H.D. Xie, H. Chai, Y.T. and Guan, Z.T. (2017) An exploration of the role of a fish-oriented diet in cognitive decline: a systematic review of the literature. *Oncotarget*, **8**(24), pp.39877-39895.

Zepeda, L. and Deal, D. (2009) Organic and local food consumer behaviour: Alphabet Theory,

International Journal of Consumer Studies, **33**, pp. 697-705.

Zhang, J. Sasaki, S. Amano, K. and Kesteloot, H. (1999) Fish consumption and mortality from all causes, ischemic heart disease, and stroke: an ecological study, *Preventive medicine*, **28**(5), pp. 520-529.

Zhang, M. Picard-Deland, E. and Marette, A. (2013) Fish and marine omega-3 polyunsaturated fatty acid consumption and incidence of type 2 diabetes: a systematic review and meta-analysis. *International Journal of Endocrinology*, **2013**, pp.1-12.

Zhang, Y. Chen, J. Qiu, J. Li, Y. Wang, J. and Jiao, J. (2016) Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. *American Journal of Clinical Nutrition*, **103**(2), pp. 330-340.

Zhang, Y. Zhuang, P. He, W. Chen, J.N. Wang, W.Q. Freedman, N.D. Abnet, C.C. Wang, J.B. and Jiao, J.J. (2018) Association of fish and long-chain omega-3 fatty acids intakes with total and cause-specific mortality: prospective analysis of 421 309 individuals. *Journal of internal medicine*, **284**(4), pp.399-417.

Zhao, L.G. Sun, J.W. Yang, Y. Ma, X. Wang, Y.Y. and Xiang, Y.B. (2016) Fish consumption and all-cause mortality: a meta-analysis of cohort studies. *European journal of clinical nutrition*, **70**(2), p.155-162.

Zhao, W. Tang, H. Yang, X. Luo, X. Wang, X. Shao, C. and He, J. (2019) Fish Consumption and Stroke Risk: A Meta-Analysis of Prospective Cohort Studies. *Journal of Stroke and Cerebrovascular Diseases*, **28**(3), pp.604-611.

Zheng, J. Huang, T. Yu, Y. Hu, X. Yang, B. and Li, D. (2012) Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. *Public Health Nutrition*, **15**(4), pp.725-737.

Zheng, J.S. Huang, T. Yang, J. Fu, Y.Q. and Li, D. (2012) Marine N-3 polyunsaturated fatty acids are inversely associated with risk of type 2 diabetes in Asians: a systematic review and meta-analysis. *PloS one*, **7**(9), p.e44525.

Zheng, J.S. Hu, X.J. Zhao, Y.M. Yang, J. and Li, D. (2013) Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. *BMJ*, **346**, pp.1-10.

Zhihui, W. Weihua, Y. Zupei, W. and Jinlin, H. (2016) Fish consumption and risk of breast cancer: meta-analysis of 27 observational studies. *Nutricion Hospitalaria*, **33**(3), pp.703-712.

Zhuang, P. Wang, W. Wang, J. Zhang, Y. and Jiao, J. (2018) Current Level of Fish Consumption is Associated with Mortality in Chinese but not US Adults: New Findings from Two Nationwide Cohort Studies with 14 and 9.8 Years of Follow-Up. *Molecular nutrition & food research*, **62**(8), p.1700898.

APPENDICES

APPENDIX 1: ETHICAL APPROVAL LETTER FROM THE RESEARCH ETHICS COMMITTEE OF THE FACULTY OF EDUCATION, HEALTH AND WELLBEING, UNIVERSITY OF WOLVERHAMPTON

UNIVERSITY OF WOLVERHAMPTON

Dr Alexandra Hopkins RN PhD MSc MBA RNT RCNT DANS
Dean of the Faculty of Education Health and Wellbeing

University of Wolverhampton
Walsall Campus
Gorway Road
Walsall
WS1 3BD
United Kingdom

Telephone Codes
UK: 01902 Abroad: +44 1902

Switchboard: 321000

Internet: www.wlv.ac.uk

4th July 2018

Aishat Bakre

University of Wolverhampton

FEHW

Dear Aishat

Re: Impact of fish consumption on the risk of dementia: A focus group research (Health Professions, Psychology, Social Work & Social Care)

The Faculty Ethics Panel (Health Professions, Psychology, Social Work & Social Care) has considered and reviewed your submission**.**

On review your Research Proposal was passed and the Panel believes that the ethical issues inherent in your study have been adequately considered and addressed. The committee commented that this is a much better submission and the only corrections needed are proof reading and grammar checks. Therefore, the Panel is giving you full ethical approval for your study (Code 1 - Approved). We would like to wish you every success with the project.

We would like to wish you every success with the project.

Yours sincerely

Angela Clifford

Dr Angela Clifford (BSc, MSc, PhD, CPsychol)

Chair – Ethics Panel

APPENDIX 2: APPROVAL LETTER TO RECRUIT PARTICIPANTS FROM THE ORGANISATION

Letter redacted due to confidentiality considerations.

APPENDIX 3: REQUEST LETTER FOR RECRUITMENT OF PARTICIPANTS

Dear ………….

As part of my PhD study in Public Health at the University of Wolverhampton, I am planning to conduct a research on the "Impact of fish consumption on the risk of dementia and the factors affecting its consumption in older adults". For this research to be successfully conducted, I will need the assistance of your organisation to recruit participants for the study. If you accept my request to assist, it will involve allowing me to recruit few older adults aged 60 years and above for a focus group discussion, and if possible, conduct the study at your organisation. Although there are no direct benefits, but it will help explore the views of older people about the impact of fish consumption on dementia and the factors influencing its consumption. This will help to improve the knowledge and understanding of the association between fish consumption and the risk of dementia and guide strategies to reduce or prevent dementia in the society.

Therefore, I am writing to ask for your permission and the assistance of your organisation to recruit participants for the study. A copy of the research protocol is enclosed for your perusal, but further details about this research will be provided if required. I look forward to your favourable consideration.

Yours sincerely,

Researcher Signature

APPENDIX 4: PARTICIPANT INVITATION LETTER

Dear ……….

We are writing to invite you to participate in a research project, which we are conducting as part of an ongoing PhD study in Epidemiology and global health at the University of Wolverhampton. Additional information is enclosed which explains the title and aims of the project and what taking part will involve. If you are interested in participating in either of the focus group discussions, you will be part of 6-8 participants that indicate interest. The discussion would take between 60-90 minutes. Anything you say would be totally confidential and any notes made as a result of the discussion would be destroyed afterwards.

The focus group would take place at the University of Wolverhampton at a stipulated time and date that will be communicated to you. Findings will be reported, but no identifying facts about you will be shown, instead numbers will be used to replace the names.

If you feel that you would like to be part of the discussion or would like further information, please contact the researcher on [redacted]. If you would prefer not to be involved, please destroy/ignore this letter.

Yours sincerely,

Aishat Bakre

Signed

APPENDIX 5: FOCUS GROUP DISCUSSION GUIDE

Introductions (to build rapport)

- Welcome, introduction and overview of the project

- Explanation of the purpose of the interview, participant selection criteria and how information will be used

- Reminder that the interview will be audio recorded

Icebreaker – please could you tell me about your current fish consumption habits? What do you eat and how often?

Key themes

1. Do you think eating fish is beneficial to peoples' health particularly at old age? If so

Prompt

- What kind of potential health benefit can older people derive from eating fish?

2. Do you think that eating fish reduces health problems such as cardiovascular diseases and dementia that affect people? If so

Prompt

- Why do you think so?
- How many days in a week should fish be eaten? Should it be eaten once a week, more than twice a week or ≥Once a day?
- Why do you think so?
    - How can eating fish reduce the risk of dementia?

3. What factors make you choose to eat fish over other source of protein?

Prompt

- Which of the factors mentioned above does have the greatest impact on your choice of eating fish?
- In your view, what factors hinders eating fish in older people?
- What factors enables eating fish in older people?
    - Income, married, educational level, occupational class, gender

Ending

4.Do you have any comments, recommendation and addition to the topic of discussion about your perception on the health benefit of eating fish and the factors that can affect its consumption?

Question Guide	Reason
Introduction	To build rapport
Key themes	
Do you think eating fish is beneficial to peoples' health particularly at old age? If so	To better understand if participants know that eating fish could help them stay healthy as they get older and the kind of health benefit they can derive from its consumption.
Do you think that eating fish reduces health problems such as cardiovascular diseases and dementia that affect people	To better understand if participants are aware that eating fish can help to reduce the risk of cardiovascular diseases and dementia specifically.
What factors makes you choose to eat fish over other source of protein?	To understand the reason why the participants', choose to eat fish. Also, to know the list of factors that affects their level consumption. .

APPENDIX 6: A BRIEF QUESTIONNAIRE

Age (years)
40-44 ☐
45-49 ☐
50-54 ☐
55-59 ☐
60-64 ☐
65-69 ☐
70-74 ☐
75-79 ☐
≥80 ☐

Sex
Male ☐
Female ☐

Educational background
Primary School ☐
Secondary School ☐
University Degree ☐
Graduate Degree ☐
Other
Please specify:
……………………………………………

Occupation
Public sector ☐
Private sector ☐
Self employed ☐
Retired ☐
No formal job (including business/other/housewife) ☐

Income class (£/month)
800-1000 ☐
1000-3000 ☐
>3000 ☐

Marital status
Married ☐
Never married ☐
Widow ☐
Divorced ☐

Ethnic background
White British ☐
☐

Black British
Black African ▢
Black Caribbean ▢
Indian ▢
Pakistani ▢
Bangladeshi ▢
Chinese ▢
Asian Other ▢
Please specify:
…………………………………………….
Any other Ethnic group ▢

Please specify:
………………………………………….....

Do you have any Children?

None ▢
1 ▢
2 ▢
3 ▢
4 ▢
>4 ▢

Do you have any children under 18years, living with you?

Yes ▢
No ▢

APPENDIX 7: CONSENT FORM

Title of Project: People's perceptions of fish consumption and its associations with health

Name of Researcher: Aishat T. Bakre

Please initial boxes

1. I confirm that I have read and understand the information sheet dated ………………2018 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐
3. I understand that my data will be stored securely and confidentially and that I will not be identifiable in any report or publication ☐
4. I understand that the researcher may wish to publish this study and any results found, for which I give my permission ☐
5. I agree for my focus group to be tape recorded and for the data to be used for the purpose of this study. ☐
6. I agree to take part in the above study. ☐

………………………..	……………………..	…………………………
Name	Date	Signature
………………………..	……………………..	…………………………
Name of person taking consent (if different from researcher, state position)	Date	Signature
………………………….	…………………….	…………………………
Researcher	Date	Signature

APPENDIX 8: PARTICIPANT INFORMATION SHEET

Study title

People's perceptions of fish consumption and its associations with health

I would like to invite you to participate in a research study. Before you decide to participate, it is crucial for you to understand why the research is being done and what it will entail. Please ensure you read the following information sheet carefully and discuss it with others (friends or relatives) if you wish. Please ask the researcher if there is anything that is not clear, or you would like more information. Take time to decide if you wish to participate. Thank you for reading this.

What is the purpose of the study?

This research is being undertaken as part of my PhD study. I am interested in exploring the perceptions of people aged 60 years and over about the health benefit of fish consumption and the determining factors that can affect its consumption.

Why have I been chosen?

You have been invited to take part in this study because your age falls into our target age group of adults in the chosen area for data collection. You will be part of 6-8 other participants that agrees to take part in the study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You can withdraw from the study at any time. After the focus group, you can withdraw your data up until the commencement of the data analysis which should begin one week after the completion of the focus group discussion.

What will happen if I decide to take part?

If you decide that you want to take part in the study, you will be invited to participate in a focus group discussion that will involve a meeting of a group of 6 to 8 people at the University of Wolverhampton City Campus. This should last between 60-90 minutes. You will be asked to partake in a group discussion, where questions will be asked about your views and perceptions on the health benefit of fish consumption and the determining factors that can affect its consumption. Before the commencement of the focus group, you will be asked to complete a brief demographic questionnaire. This discussion will be facilitated by the researcher (moderator) and a co-moderator. The two moderators will take notes throughout the discussions and ensure all the participants are encouraged to speak and their views are well documented. These discussions will be audiotaped with the consent of the participants.

What are the potential benefits and risks of taking part?

There are no direct benefits for you if you take part. However, by taking part you will help us to better understand peoples' views and perceptions on the health benefit of fish consumption and the determining factors that can affect its consumption.

There are no known risks associated with participating in this study. However, you may feel uncomfortable when participating in the discussion. The researcher will do all they can to ensure a comfortable environment is provided to conduct the focus group discussion. In addition, if you would like to take time out of the discussion, please simply indicate to the researcher.

Will my taking part in the study be kept confidential?

Yes. The ethical and legal rules will be followed and all the information about your participation in this study will be kept strictly confidential. The transcription of the discussion you participate in and the brief questionnaire you completed will be stored on a password protected computer in a locked office. Only the researcher will have access to the information. You will not be identified in any publication or report as all identifying information will be removed.

What will happen at the end of the research study?

The results will be submitted as part of a research dissertation towards a PhD in epidemiology and global health. Also, it will be presented at international conferences and published in scientific journals. The collected information will be securely kept in a locked location for 2 years according to the university regulation on data storage and subsequently destroyed.

What if I have a problem or concern?

If you have a concern about any aspect of this study, you should ask to speak with the Associate Dean of the Faculty of Education Health and Wellbeing (FEHW) who will do his best to answer your questions. Please contact Dr. Ranjit Khutan on [redacted] or [redacted].

Who has reviewed the study?

The University of Wolverhampton Research Ethics Committee(s) will review the study.

Contact for further information

If you have any other questions about this research study, you may contact my supervisor Prof. Rouling Chen at [redacted] or on [redacted], or Aishat T. Bakre at [redacted]

Thank you for considering taking part and taking time to read this information sheet.

Kind regards,

Aishat Bakre

APPENDIX 9: FOCUS GROUP DISCUSSION TRANSCRIPT SPECIMEN

Icebreaker-Please could you tell me about your current fish consumption habits? What do you eat and how often?

P1: You can love, So what I eat tinned mackerel em at least probably once a week, I will eat tinned salmon emm probably once twice a month, and Emm well since I have moved to Wolverhampton and probably not eating as much fresh fish as I eat in Galway, but emm I will buy cod and haddock and things like that as well yes.

P2: Yes, I probably eat fish twice a week. Is not anything particularly special? The equivalent to fish fingers. It might be just you know breaded fillet. Emm may be twice a week. In the menu it may be cod, or I think they call it haddock yes you know it is a sort of cheap fish, but then twice a week or two portions a week.

P3: emm I can eat quite a lot of fish. It is a factor of the Mediterranean as well. In my diet as a child, I always had fish in my diet. So, I have always loved it as a child. Mainly kippers, I like as well oily fishes' kippers, emm but then you get the cod and …Mediterranean Sea as well…. Haddock but now it's difficult to find fresh fish I find anywhere; you can't get it anywhere. We do get the frozen one, which we find sometimes that it is. My son is a big eater of fish as well. We like emm fish, shellfish as well, prawns, mussels, crab, anything like that, and we like sea food and pasta. We love eating a lot of pasta as well, with a lot of seafood in it. So, is quite I am a big big fan of fish?

P4: Well last time, I said we eat we ate because is part of our menu in Africa. We eat food, soup whatever thing we do most of the time fish is involved. But since after the last discussion, I must confess that I have increased my own personal consumption. That is one of the benefits I got from the discussion. Now I don't care whether my wife prepares it or not, I go to the market, I buy fish, I cut it, however I make it, I enjoy it. Owing to my age, am there, so I need to consume like this, very delicious. One problem as he mentioned, how do we know which is the fresh fish. Everything we see in the market most of them are produced you know in a certain way and are frozen. So now I consume it more often than before.

Q What type of fish do you really love to eat. Is it oily or lean fish or just any kind?

P1: Oily, I suppose the main mackerel and salmon, emm prawns I do like prawns, and may do cod as well, but mainly probably oily fish.

P3: I do oily fishes. I do like kippers. Emm Is salmon referred to as oily fish? salmon, and tuna. So those are my main three oily ones, and then obviously I got cod, haddock, plaice and then you get seafoods like prawns, mussels. I don't know if mussels' or things like that are classified as seafoods and my son is a big fan of all those fish as well.

Moderator: I think you do both oily and lean fish

P3: yes

P2: I will eat any fish. Mackerel, crab. Currently am only eating white fish. But emm is not the right thing to be eating, but to be absolutely honest, I find with the oily fish it causes a lot of smell in the kitchen, and the way my present kitchen is, is a new kitchen to me. Is really difficult to deal with. If I can get a place outside where I could sort of barbeque some, is something I will be very very happy.

P4: The more handy fish I eat a lot now is tuna. **Is it because is ca**nn**ed**, yes you know you can always get it. You need less fatigue to prepare it. Just open it, add it in your salad or whatever. I consume it a lot. So, when I go to the market, I always buy the big tilapia fish. The cut one**,** no no, I do everything in my house, I cut it myself, then I prepare it. Yes, is very nice.

P5: Both oily and lean fish, but I eat oily fish. Mackerel I love. In any way I love mackerel, whether it is smoked or fresh and cutting, you know actually I am a fisher woman. My husband was a fisherman and I used to fish, and my dad was a fisherman, so he used to bring fish home, we used to. So, you eat it well.

P6: I eat both. I eat lesser oily than normal fish but will like to eat more oily fish for specific reason.

Moderator: reiterate lesser oily fish

Q Do you think eating fish is beneficial to peoples' health particularly at old age?

P1: Is something I haven't thought of in terms of age until until Isaac mentioned this. Emm emm Yes, there is some evidence to say that oily fish does help with memory, however, a lot of it haven't been disapproved recently and the saying having been approved to say that, but that's really long. Emm, so I eat fish because I believe in eating various diet and fish is part of them and that is the main reason why I eat it. Not for actual any really other purpose other than just to eat various diet.

P3: Is very conflicting whose, I am more than convinced for all that is written that is very good for your diet regardless of what age. Am not sure, am convinced it is good for your old age, because of the studies and the things you've heard. What I can't just say is that you get conflicting research that says actually is not that good for your age or your mind or is about your age or your mind. But am convinced overall is still good to have it in your diet whatever age mainly even when you get either even more older.

P2: …………. because it was cheap, kippers, and herrings, sprats, sardines, oily fish mackerel, not so cheap, but those the herrings and sprats was so certain, and sardines is very cheap indeed, so that's what we ate. Am sort of assuming am not remembering very well. I will imagine my parent live in more of a central ….. and at that time and I think that still stands, the whole lifestyle was fish is good for your brain, yes that is what I have always heard. Now usually this is not maybe scientifically sound. Usually there is an element of truth in this whole lifestyle, so that is my thinking that it is a good thing for you, from your youth right to adult. I think it is a good diet fish.

P4: Well, the assumption has always remained that fish is emm good for old people for everybody especially for aged people. One of the reason I believe is emm fish is not fatty, and whenever old person, person of certain age goes to the hospital or doctor one of the first things they check is your age your weight, so they will ask you to be careful with your weight and then being careful involve not taking things of fatty food, so fish is one of the things that doesn't contain fat. It is not hard to chew for those who doesn't who don't have teeth. Is not hard to chew, is not hard to digest, so and then it helps the brain as generally agreed or assumed.

P6: Yes, going on to dementia, they do say it sort of help with dementia. The risk of. Not saying you won't get it at all, it should reduce the risk of dementia. And it is good for it.

P5: Well I am not sure, how useful it is for the risk of dementia. My mother had Alzheimer's and from being very very young they were not short of money and they had fish. Growing up I did, growing up my husband did, and he had dementia from his 60's. My mother was in her 60's, early 60's. I think formal things attributed to smoking possibly drinking I don't know if not because I drink. So, I don't know really. I am not sure about that. I think it is important, I think the good thing about eating fish is you got to……… that is the very best thing that I think.

Prompt: What kind of potential health benefit specifically do you think we can derive from eating fish?

P1: Well, I really don't know, I mean am guessing, but just as David said that perhaps there is element that it is good for your health and is good for your brain, but apart from that I really don't know.

P3: Am thinking yes, it is definitely good for your health and for your brain. Am pretty sure of that, because the research is done and for elderly people, but whether it helps with certain illness including dementia and Alzheimer's. How much does it actually help to prevent or even get better or not certainly get better, but to prevent actually, because there is a lot of research that might consider that it could be hereditary the dementia regarding how much fish you eat. Is it truly you going to get it regarding how much fish you eat or you going to delay getting it, that could help as well? So, there is a lot of questions whether the maximum benefit you can get from a fish, is eating fish all the time. It definitely will be, it will be taken anyway regardless of what because there is still some benefit in it. That is my question, will it stop dementia, will it slow down dementia

P2: What is the exact question is it benefit. Is simple to eat and we believe there is the broken …… so dementia or not it cannot be beneficial for you, fish I don't think, but if it helps dementia that is an add-on is a bonus.

P4: A lot of health benefit. Dementia is the target of everybody and fish, so we really believe unless proven otherwise that fish help you know the problem of dementia even sight, eyesight, see then weight loss, or weight control, fish is involve, then is all depending generally not only on fish on other ways people live their life, because some people say they say cigarette kills, but I know people who has started smoking from childhood, they are 80, 90 they still smoke, I see.

APPENDIX 10: IMPACT OF FISH CONSUMPTION ON INCIDENT DEMENTIA IN OLDER PEOPLE: A SYSTEMATIC LITERATURE REVIEW OF COHORT STUDIES

Following the method of the previous systematic literature review in chapter 4 conducted since November 2016, an updated review was conducted from the earliest date of the databases to 30 September 2019.

Methods

Data Sources and Studies selection process

The MEDLINE, PubMed, CINAHL, PsychINFO, and Psychology and Behavioural Sciences Collection databases were independently searched and re-searched to retrieve suitable articles. The strategy for the database search was developed using the PEO (Population, Exposure and Outcome) framework (Moher *et al.*, 2009). The search terms were [‘dementia’ OR ‘Alzheimer’s disease’] AND [‘fish’]. The search for relevant articles included only cohort studies with no language restriction. The title and abstract for each of the searched studies were read and studies appropriate for the current review were selected if they investigated an association between fish consumption and dementia (or Alzheimer’s disease (AD)) in the population. Alongside the electronic database search, a manual reference search was also conducted to retrieve other articles missed by the online search. If two articles were published from the same cohort data but in different follow-up durations (Kalmijn *et al.,* 1997; Barberger-Gateau *et al.,* 2007; Devore *et al.*, 2009; Ngabirano *et al.,* 2019), we used the article from the longest follow-up study for review (Devore *et al.*, 2009; Ngabirano *et al.,* 2019). Figure 1 shows the study selection process. Nine original studies were identified eligible for review. Following the PRISMA (Preferred Reporting

Items for Systematic reviews and Meta-Analyses) guidelines (Moher *et al.,* 2009), a systematic review was conducted.

Data extraction and Quality assessment

Each of the articles was reviewed by two reviewers (Aishat Bakre and Isaac Danat) and assessed independently using a predesigned data extraction form to extract the necessary information from the chosen studies. The information extracted includes the first author's name, publication year, study type, study name, study location, participants' characteristics, recruitment strategy, sample size, sample size at follow up (% of baseline sample), study duration, baseline measure of frequency of fish consumption, categories of comparison, endpoint outcomes: number of dementia cases; dementia diagnosis criteria, data analysis method, confounders adjusted, and findings including the RRs, ORs, HRs and 95% CIs of dementia and AD. Differences in reviewing literature and extracting data between the two reviewers were resolved through face-to-face discussion; if differences remained, a third reviewer discussed with them to reach agreement. The quality assessment of the articles was achieved by employing the Newcastle-Ottawa Scale (Wells *et al.*, 2014). The Newcastle-Ottawa Scale (NOS) (Wells *et al.*, 2014) nine components rating scale assesses each article on three broad scales. This assesses the selection bias, comparability and outcome/exposure. Based on specific criteria, a total award of between 0-6 scores was classified as a low-quality study, while 7-9 scores were classified as a high-quality study.

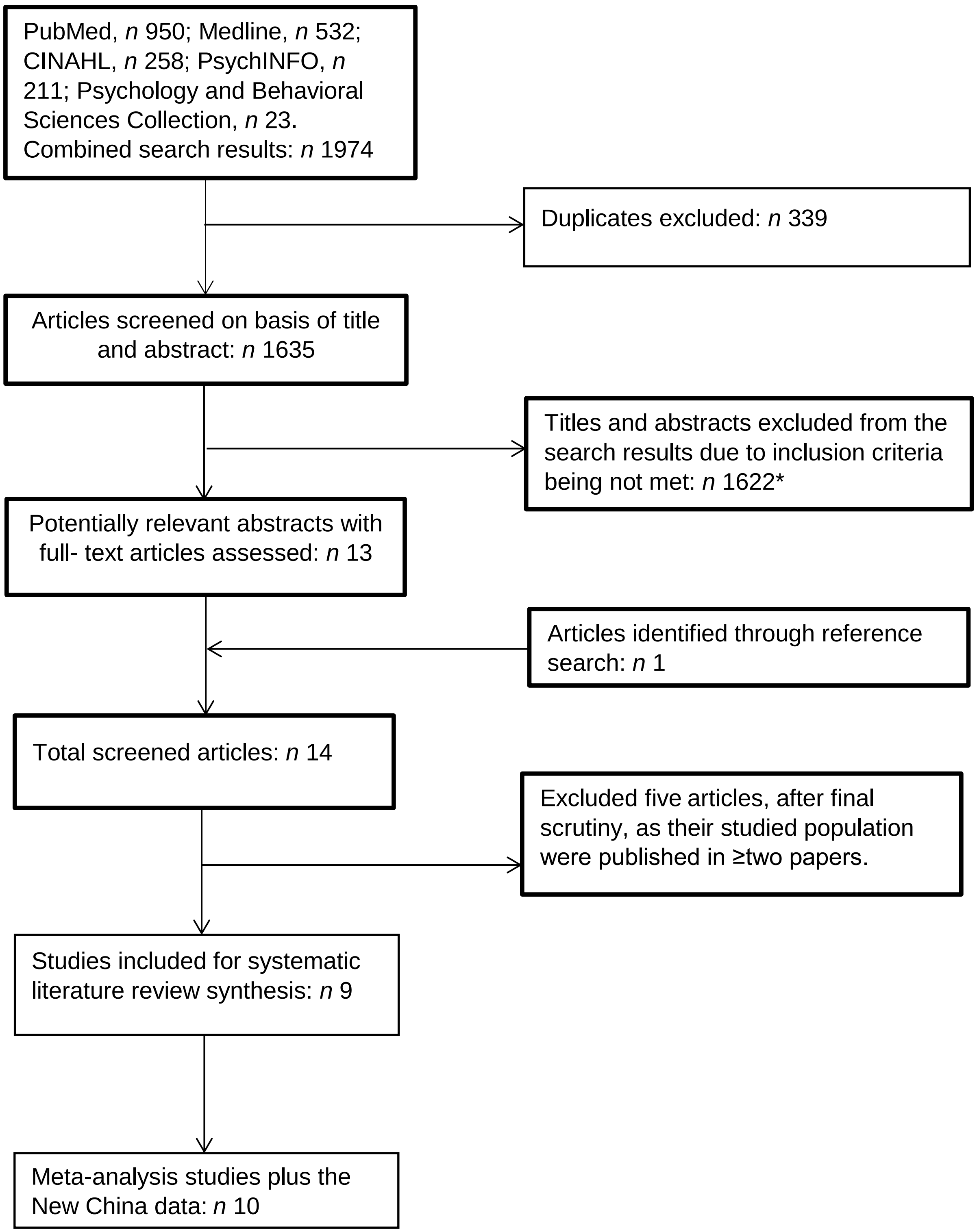
Results

Synthesis of the studies

In the nine identified articles, we found that all were from high income countries, except for one study (Tsurumaki *et al.,* 2019) from LMIC. They were published between 2002 and 2019 (Barberger-Gateau *et al.*, 2002; Morris *et al.*, 2003; Huang *et al.*, 2005; Schaefer *et al.*, 2006;

Devore *et al.*, 2009; Lopez, Kritz-Silverstein, Barrett-Connor, 2011; Fischer *et al.*, 2018; Ngabirano *et al.*, 2019; Tsurumaki *et al.*, 2019). Their sample size varied from 242 to 13102, with a total of 32247 participants, and the minimum age in these studies varied from 55 to 82 years. A food frequency questionnaire (FFQ) was used in five of the studies (Barberger-Gateau *et al.*, 2002; Morris *et al.*, 2003; Huang *et al.*, 2005; Ngabirano *et al.*, 2019; Tsurumaki *et al.*, 2019), and a semi quantitative FFQ (SFFQ) was used in the other two (Schaefer et al., 2006; Lopez, Kritz-Silverstein, Barrett-Connor, 2011). A meal-based check list alongside an SFFQ was used in one (Devore *et al.*, 2009), while Fischer *et al.* (2018) used a brief "cognitive health" food intake screener. Two of the studies reported a statistically significant association of fish consumption with reduced risk of dementia. Data from four studies showed an association but a non-statistically significant reduction, while three exhibited no association (Devore *et al.*, 2009; Fischer *et al.*, 2018; Ngabirano *et al.*, 2019). Table 4.2 (see Chapter 4) documents the details of the studies' characteristics and outcomes. We examined the quality of each of these studies and found that the quality of these articles was in general good (See Table 1).

Figure 1: Flowchart showing the literature search technique



*Reasons for exclusions: appropriate outcome not reported, randomized control trial; assessed another exposure other than fish; assessed another outcome other than dementia or Alzheimer's disease; articles on importance of fish to dementia and brain development; news briefs, articles on elderly nutrition; literature review/meta-analysis; presentation; cross-sectional study; case-control study

Table 1. Quality assessment for the 9 articles identified that studied the impact of fish consumption on incident dementia.

Study	1	2	3	4	5	6	7	8	9	10
Ngabirano *et al.* 2019	★	★	★	★	★	★	★	★	★	★
Tsurumaki *et al.* 2019	★	★	★	★	★	★	★	★	★	★
Fischer *et al.* 2018	★	★	★	★	★	★	★	★	★	★
Barberger-Gateau *et al.* 2002	★	★		★	★	★		★		★
Devore *et al.* 2009	★	★	★	★	★	★	★	★	★	★
Huangs *et al.* 2005	★	★	★	★	★	★	★	★	★	★
Lopez *et al.* 2011		★	★		★	★	★	★	★	★
Morris *et al.* 2003	★	★	★	★	★	★	★	★	★	★
Schaefer *et al*. 2006	★	★	★	★	★	★	★	★	★	★

(1) Cohort truly representative (2) Controls derived from the same cohort (3) Clear measurement of fish consumption at baseline (4) Adequacy of Follow-up duration (≥12 months) (5) Reliable methods of dementia and AD diagnosis (i.e., Quality of outcome) (6) Cohort data analysis controlled for age, sex and educational level (7) Cohort data analysis controlled for other confounders (8) Findings interpreted well (9) Weakness mentioned and explained clearly (10) Paper written well.

APPENDIX 11: SYNTAX FOR DATA ANALYSIS IN CHAPTERS

Chapter 5

```
CROSSTABS
  /TABLES=sex BY a1122fourlevel
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.

LOGISTIC REGRESSION VARIABLES a1122fiseattoge
  /METHOD=ENTER Age_group sex BMICUT
  /CONTRAST (Age_group)=Indicator(2)
  /CONTRAST (sex)=Indicator(2)
  /CONTRAST (BMICUT)=Indicator(2)
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES a1122fiseattoge
  /METHOD=ENTER Age_group sex waistcut smoke01 urban_rural
  /CONTRAST (Age_group)=Indicator(2)
  /CONTRAST (sex)=Indicator(2)
  /CONTRAST (waistcut)=Indicator(1)
  /CONTRAST (smoke01)=Indicator(1)
  /CONTRAST (urban_rural)=Indicator(1)
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).


DATASET ACTIVATE DataSet1.
CROSSTABS
  /TABLES=sex BY a1122fiew3
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.

RECODE a1122 (0=0) (1=1) INTO a1122aweek.
VARIABLE LABELS a1122aweek 'a1122aweek'.
EXECUTE.
```

```
CROSSTABS
  /TABLES=sex BY a1122aweek
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

Chapter 6
Syntax for meta-analysis

RR Ln SE Computing for meta-analysis

```
Compute LnRR=ln (RR).
compute LnRR_95L=Ln (RR_95L).
compute LnRR_95U=Ln (RR_95U).
Compute SeLnRR= (ln (RR_95U)-Ln (RR_95L))/2/1.96.
execute.
```

Stata Do file for meta-analysis

```
metan LnRR SeLnRR if group ==4, label(namevar=study_id) random effect (Relative Risk) eform
metan LnRR SeLnRR if group ==4, label(namevar=study_id) fixed effect (Relative Risk) eform
metan LnRR SeLnRR if Selection ==1, label (namevar=Author, yearvar=PubYear) random effect (Relative Risk) eform

metafunnel LnRR SeLnRR if Selection ==1, xlabel (0.1 0.2 0.4 0.6 0.8 1 2 3 4 5 10 20) xtitle (Relative Risk) eform

metabias LnRR SeLnRR if Selection ==1, egger
```

Chapter 7

```
USE ALL.
COMPUTE filter_$=(province<=4 & a1122<=4 & DEM1066_rc=0 & fiveP6071followup<2).
VARIABLE LABELS filter_$ 'province<=4 & DEM1066_rc=0 & fiveP6071followup<2 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
```

```
FREQUENCIES VARIABLES=a1122fourlevels
  /ORDER=ANALYSIS.

CROSSTABS
  /TABLES= a1122fourlevels by Dem6071W2a
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.

CROSSTABS
  /TABLES= a1122fourlevels BY Dem6071W2a
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COLUMN
  /COUNT ROUND CELL.

DATASET ACTIVATE DataSet3.
RECODE a1122fourlevels (0=0) (1=0) (2=2) (3=3) INTO a1122comblevel0and1.
VARIABLE LABELS a1122comblevel0and1 'fishcomblevel0and1'.
EXECUTE.

/*a1122 a1122comblevel0and1 district province sex_rc age_yao a4
BMICategoriesNomissing smoke_for_cur_wz drinking_for_cur_wz marriage
c6Nomissing hypertesion140yes ADL_group a1121Nomissing a1123Nomissing

/* a1122comblevel0and1 district province sex_rc age_yao a4 BMICategoriesNomissing
smoke_for_cur_wz drinking_for_cur_wz marriage c6Nomissing hypertesion140yes b5
b6 b2 b12Nomissing DepressionGMS ADL_group a1121Nomissing a1123Nomissing
    a1124Nomissing a1125Nomissing


LOGISTIC REGRESSION VARIABLES Dem6071W2a
  /METHOD=ENTER a1122comblevel0and1 district province sex_rc age_yao a4
BMICategoriesNomissing smoke_for_cur_wz
    drinking_for_cur_wz marriage c6Nomissing hypertesion140yes b5 b6 b2
b12Nomissing DepressionGMS ADL_group a1121Nomissing a1123Nomissing
    a1124Nomissing a1125Nomissing
  /CONTRAST (a1122comblevel0and1)=Indicator(2)
  /CONTRAST (district)=Indicator(1)
  /CONTRAST (sex_rc)=Indicator(1)
  /CONTRAST (a4)=Indicator(1)
  /CONTRAST (province)=Indicator(1)
```

```
 /CONTRAST (BMIcategoriesNomissing)=Indicator(1)
 /CONTRAST (smoke_for_cur_wz)=Indicator(1)
 /CONTRAST (drinking_for_cur_wz)=Indicator(1)
 /CONTRAST (marriage)=Indicator(1)
 /CONTRAST (c6Nomissing)=Indicator(1)
 /CONTRAST (hypertesion140yes)=Indicator(1)
 /CONTRAST (b6)=Indicator(1)
 /CONTRAST (b2)=Indicator(1)
 /CONTRAST (b5)=Indicator(1)
/CONTRAST (b12Nomissing)=Indicator(1)
 /CONTRAST (ADL_group)=Indicator(1)
 /CONTRAST (DepressionGMS)=Indicator(1)
 /CONTRAST (a1121Nomissing)=Indicator(1)
 /CONTRAST (a1123Nomissing)=Indicator(1)
 /CONTRAST (a1124Nomissing)=Indicator(1)
 /CONTRAST (a1125Nomissing)=Indicator(1)
 /PRINT=CI(95)
 /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).
```

```
RECODE b12 (0=0) (1=1) (SYSMIS=999) (8 thru 9=999) INTO b12Nomissing.
EXECUTE.
```

a1122fourlevel

```
RECODE a1122fourlevels (0=0) (1 thru 2=1.2) (3=3) INTO a1122fourlevel3.
EXECUTE.
```

```
DATASET ACTIVATE DataSet1.
SORT CASES BY sex_rc.
SPLIT FILE LAYERED BY sex_rc.
```

RR Ln SE Computing for meta-analysis

```
Compute LnRR=ln (RR).
compute LnRR_95L=Ln (RR_95L).
compute LnRR_95U=Ln (RR_95U).
Compute SeLnRR= (ln (RR_95U)-Ln (RR_95L))/2/1.96.
execute.
```

Stata Do file for meta-analysis

```
metan LnRR SeLnRR if group ==4, label(namevar=study_id) random effect (Relative Risk) eform
metan LnRR SeLnRR if group ==4, label(namevar=study_id) fixed effect (Relative Risk) eform
metan LnRR SeLnRR if Selection ==1, label (namevar=Author, yearvar=PubYear) random effect (Relative Risk) eform

metafunnel LnRR SeLnRR if Selection ==1, xlabel (0.1 0.2 0.4 0.6 0.8 1 2 3 4 5 10 20) xtitle (Relative Risk) eform

metabias LnRR SeLnRR if Selection ==1, egger
```

Chapter 8

```
USE ALL.
COMPUTE filter_$=(death_AB<3 and province<6 and a1122<5).
VARIABLE LABELS filter_$ 'fiveP6071followup<3 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.

CROSSTABS
  /TABLES=sex_rc BY death_AB
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.

CROSSTABS
  /TABLES=sex_rc BY death_AB
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COLUMN
  /COUNT ROUND CELL.

RECODE a1122 (0=0) (1=1) (2=2) (3=3) (4=3) INTO a1122new.
VARIABLE LABELS a1122new 'fish4levels'.
EXECUTE.

COXREG FT5province1
```

```
  /STATUS=death_AB(2)
  /CONTRAST (a1122new)=Indicator(1)
  /METHOD=ENTER a1122new
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).

COXREG FT5province1
  /STATUS=death_AB(2)
  /CONTRAST (a1122new)=Indicator(1)
  /CONTRAST (age_yao)=Indicator(1)
  /CONTRAST (sex_rc)=Indicator(1)
  /METHOD=ENTER a1122new sex_rc age_yao
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).

DATASET ACTIVATE DataSet1.
RECODE a1122 (0=0) (1=1) (2=2) (3=2) (4=2) INTO fish3levels.
VARIABLE LABELS fish3levels 'a1122third'.
EXECUTE.

USE ALL.
COMPUTE filter_$=(death_AB<3 and province<6).
VARIABLE LABELS filter_$ 'fiveP6071followup<3 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.


USE ALL.
COMPUTE filter_$=(DementiaGMS=3.50).
VARIABLE LABELS filter_$ 'DementiaGMS=3.50  (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.

USE ALL.
COMPUTE filter_$=(DementiaGMS=.00).
VARIABLE LABELS filter_$ 'DementiaGMS=.00  (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
```

```
COXREG FT5province1
  /STATUS=death_AB(2)
  /CONTRAST (fish3levels)=Indicator(1)
  /METHOD=ENTER fish3levels
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).

COXREG FT5province1
  /STATUS=death_AB(2)
  /CONTRAST (fish3levels)=Indicator(1)
  /CONTRAST (age_yao)=Indicator(1)
  /CONTRAST (sex_rc)=Indicator(1)
  /METHOD=ENTER fish3levels age_yao sex_rc
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).


COXREG FT5province1
  /STATUS=death_AB(2)
  /CONTRAST (fish3levels)=Indicator(1)
  /CONTRAST (sex_rc)=Indicator(1)
  /CONTRAST (drinking_for_cur_wz)=Indicator(1)
  /CONTRAST (BMICategories)=Indicator(1)
  /CONTRAST (smoke_for_cur_wz)=Indicator(1)
  /METHOD=ENTER fish3levels age_yao sex_rc BMICategories smoke_for_cur_wz
drinking_for_cur_wz
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

APPENDIX 12: ETHNICITY ELEMENT OF THE STUDIES INCLUDED IN THE LITERATURE REVIEW

First Author (Publication year)	**Country of Study, Participants Ethnicity**	**Findings**
Fish Consumption and Cardiovascular Disease		
Bonaccio (2017)	Italy Central-southern Italian population	
Rhee (2017)	USA Ethnicity (Not Reported) NR	
Fish Consumption and Coronary Heart Disease		
He (2004a) Meta-analysis of 11 cohort studies		
Kromhout (1985)	Zutphen Netherlands Ethnicity-NR	
Fraser (1992)	USA Non-Hispanic white Other ethnic background	
Ascherio (1995)	USA Ethnicity-NR	
Daviglus (1997)	USA 2^{nd} and 3^{rd} generation Americans of Polish and Bohemian ancestry	
Mann (1997)	UK Ethnicity-NR	
Albert (1998)	USA Ethnicity-NR	
Oomen (2000)	Finland, Finnish Italy, Italian Netherlands, Dutch	
Yuan (2001)	China Chinese	0.68 (0.49-0.94)
Hu (2002)	USA White (98%) and Black	
Osler (2003)	Denmark Danish	
Mozaffarian (2003)	USA White and Black	

Whelton (2004) Meta-analysis of 19 observational studies		
Kromhout (1995)	Netherland Dutch	
Dolecek (1991)	USA Ethnicity-NR	
Ascherio (1995)	USA Ethnicity-NR	
Salonen (1995)	Finland Ethnicity-NR	
Rodriguez (1996)	USA (Hawaii) Japanese American	0.5 (0.28-0.91)
Daviglus (1997)	USA 2nd and 3rd Americans generation of Polish and Bohemian ancestry	
Pietinen (1997)	Finland Ethnicity-NR	
Albert (1998)	USA Ethnicity-NR	
Gillum (2000)	USA Ethnicity-NR	
Oomen (2000)	Finland, Italy, Netherlands	
Yuan (2001)	China Chinese	0.67 (0.48-0.93) low 0.51 (0.31-0.83) moderate
Hu (2002)	USA White (98%) and Black	
Osler (2003)	Denmark Ethnicity-NR	
Gramenzi (1990)	Italy Ethnicity-NR	
Siscovick (1995)	USA Ethnicity-NR	
Sasazuki (2001)	Japan Japanese	0.60 (0.4-0.9)
Tavani (2001)	Italy Ethnicity-NR	
Martinez-Gonzalez (2002)	Spain Ethnicity-NR	
Zheng (2012) meta-analysis of 17 prospective cohort studies		

Mann (1997)	UK Ethnicity-NR	
Mozaffarian (2003)	USA White and Black Americans	
Folsom and Demissie (2004)	USA Ethnicity-NR	
Ja¨rvinen (2006)	Finland Ethnicity-NR	
Yamagishi (2008)	Japan Ethnicity-NR	0.86 (0.62-1.19)
De Goede (2010)	Netherlands Ethnicity-NR	
Tomasallo (2010)	Canada White, Black and others	
Ward (2018)	USA Ethnicity-NR	
Fish Consumption and Stroke		
He (2004b) meta-analysis of 8 independent prospective studies		
Keli (1994)	The Netherlands Ethnicity-NR	
Morris (1995)	USA Ethnicity-NR	
Orencia (1996)	USA Mostly of German, Polish, Bohemian, Great Britain, and Ireland descendants	
Gillum (1996)	USA Mixed: White and Black	
Yuan (2001)	China Chinese	1.11 (0.83-1.47)
Iso (2001)	USA White (98%) and Black	
He (2002)	USA Ethnicity-NR	
Sauvaget (2003)	Japan Japanese	0.60 (0.37-0.98)
Larsson (2011) meta-analysis of 15 independent prospective studies		
Folsom (2004)	USA Ethnicity-NR	

Nakamura (2005)	Japan Japanese	1.26 (0.70-2.29)
Mozaffarian (2005)	USA White and Black	
Myint (2006)	UK Ethnicity-NR	
Wennberg (2007)	Northern Sweden Ethnicity-NR	
Yamagishi (2008)	Japan Japanese	0.91 (0.74-1.13)
Montonen (2009)	Finland Ethnicity-NR	
Larsson (2011)	Sweden Ethnicity-NR	
The remaining seven studies were already reported in He (2004b) meta-analysis above		
Xun (2012) meta-analysis of 16 cohort studies		
de Goede (2012)	The Netherlands Dutch population	
(De novo) Physicians' Health Study	USA Ethnicity-NR	
The remaining 14 studies were already reported in He (2004b) and Larsson (2011) meta-analysis above		
Zhao (2019) meta-analysis of 33 prospective cohort studies		
Kinjo (1999)	Japan Japanese	0.86 (0.79-0.94)
Kaushik (2008)	Australia Mostly Caucasian	
Takachi (2010)	Japan Japanese	
Atkinson (2011)	UK White and Black	
Bernstein (2012)	USA Ethnicity-NR	
Misirli (2012)	Greece Greek population	
Takata (2013)	China	0.63 (0.41-0.94) Ischemic stroke

	Chinese	0.90 (0.43-1.87) Hemorrhagic stroke
Kuhn (2013)	Germany German population	
Tognon (2014)	Denmark Both Danish and non-Danish origin	
Haring (2015)	USA Mixed: White and Black	
Amiano (2016)	Spain Ethnicity-NR	
Nahab (2016)	USA Mixed: White African Americans	
Bonaccio (2017)	Italy Central-southern Italian	
Farvid (2017)	Iran Iranians	
Hansen (2017)	Denmark Danish	
Wallin (2018)	Sweden Swedish	
Zhuang (2018)	USA; Ethnicity-NR China; Chinese	
Fish Consumption and Respiratory Diseases		
Chronic Obstructive Pulmonary Disease (COPD)		
Shahar (1994)	USA Black and White American	
Smit (1999) Systematic review of observational studies		
Schwartz and Weiss (1990)	USA White and Black	
Miedema (1993)	Netherlands Ethnicity-NR	
Schwartz and Weiss (1994)	USA White and Black	
Sharp (1994)	USA Japanese American	-4.4 ml (95% CI: -8.2, -0.6)

Troisi (1995)	USA Ethnicity-NR	
Hodge (1996)	Australia Ethnicity-NR	
Fluge (1998)	Norway Ethnicity-NR	
Varraso (2014)	USA Ethnicity-NR	
Asthma		
Yang (2013) meta-analysis		
Nagel (2005)	Germany Ethnicity-NR	
Li (2013)	USA White and Black	
Kim (2019)	Korea Korean population	
Fish Consumption and Cancer		
Breast Cancer		
Zheng (2013) meta-analysis of 21 prospective cohort studies (11 studies on fish intake)		
Mills (1989)	USA Non-Hispanic White Other ethnic groups	
Vatten (1990)	Norway Norwegians	
Toniolo (1994)	USA Caucasians (non-Latinas). African Americans, Latinas, and Asians	
Key (1999)	Japan Japanese	1.05 (0.82-1.35)
Cho (2003)	USA Ethnicity NR	
Gago Dominguez (2003)	Singapore Chinese Hokkien, Cantonese	0.74 (0.59-0.94)
Stripp (2003)	Denmark Danish	
Holmes (2003)	USA White and Black	

Folsom (2004)	USA Ethnicity NR	
Wakai (2005)	Japan Japanese	0.50 (0.25-1.00)
Engeset (2006)	10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom)	
Kiyabu (2015)	Japan Japanese	0.99 (0.77-1.28)
Zhihui (2016) meta-analysis of 27 observational studies		
Hislop (1986)	Canada Ethnicity NR	
Stampfer (1987)	USA Ethnicity NR	
Kato (1992)	Japan Japanese	0.81 (0.62-1.06)
Lee (1992)	Singapore Hokkien, Teochew, Cantonese Hainanese, Hakka, Other	1.0 (0.5-1.9)
Goodman (1992)	Hawaii Caucasian and Japanese	
Hirose (1995)	Japan Japanese	0.98 (0.78-1.24)
De Stefani (1997)	Uruguay Montevideo, Other counties	
Ambrosone (1998)	USA Caucasian	
Franceschi (1999)	Italy Italians	
Fernandez (1999)	Italy Italians	
Gertig (1999)	USA African Americans, Caucasian	
Mannisto (1999)	Finland Finnish	
Dai (2002)	China Chinese	1.66 (1.31-2.11)
Terry (2002)	Sweden Swedish	

Lund (2003)	Norway Norwegian	
Lund (2004)	Norway Norwegian	
McElroy (2004)	USA Ethnicity NR	
Fung (2005)	USA Ethnicity NR	
Shannon (2003)	USA White	
Shannon (2005)	China Chinese	1.55 (0.97-2.48)
Kim (2009)	South Korea Korean	0.55 (0.32-0.96)
Zhang (2009)	USA White and Black	0.72 (0.46-1.10)
Nindrea (2019) meta-analysis of 11 studies		
Kuriki (2007)	Japan Japanese	0.59 (0.31-1.12)
Murff (2011)	China Chinese	0.95 (0.75-1.20)
Sangrajrang (2013)	Thailand	0.90 (0.65-1.23)
Yaw (2014)	Malaysia Malaysian	0.81 (0.68-0.97)
Prostate Cancer		
Szymanski (2010) meta-analysis of 24 studies		
Talamini (1992)	Northern Italy Ethnicity NR	
Andersson (1995)	Sweden Swedish	
Pawlega (1996)	Poland Polish	
Key (1997)	United Kingdom White	
Fernandez (1999)	Northern Italy Ethnicity NR	
Sung (1999)	China Chinese	1.09 (0.61-1.96)
Deneo-Pellegrini (1999)	Uruguay Uruguayan	

Villeneuve (1999)	Canada West European, Asian, Aboriginal, Black, India, other	
Jain (1999)	Canada Ethnicity NR	
Jian (2004)	Southeast China	1.00 (1.17-3.86)
Sonoda (2004)	Japan Japanese	0.45 (0.20-1.02)
Chen (2005)	Taiwan Taiwanese	1.15 (0.79-1.66)
Hedelin (2007)	Sweden Swedish others	
Hu (2008)	Canada Ethnicity NR	
Mina (2008)	Canada West European East European, Asian, Indian Native, Black Other/unknown	
Amin (2008)	Canada White, Black, Asian, Hispanic Other	
Ukoli (2009)	Southern Nigeria Edo and Delta	
Mills (1989)	USA Non-Hispanic White; other ethnic groups	
Severson (1989)	Hawaii Japanese ancestry	1.22 (0.74-2.01)
Hsing (1990)	USA White	
Le Marchand (1994)	Hawaii various ethnic groups	
Schuurman (1999)	Netherland Ethnicity-NR	
Terry (2001)	Sweden Swedish	
Augustsson (2003)	USA Ethnicity-NR	
Allen (2004)	Japan Japanese	1.77 (1.01-3.11)

Park (2007)	USA African Americans Native Hawaiians Japanese Americans, Latinos, Whites	
Rohrmann (2007)	USA Ethnicity NR	
Chavarro (2008)	USA White and Black	
Allen (2008)	Europe Ethnicity NR	
Sato (2008)	Japan Japanese	0.72 (0.40-1.33)
Pham (2009)	Japan Japanese	0.12 (0.05-0.32)
Dai (2017) meta-analysis of 18 cohort &19 case-control studies		
Fradet (2009)	USA African American, Caucasian	
Richman (2010)	USA White African American, other	
Tyagi (2010)	India Asian	1.45 (1.01-2.09)
Joshi (2012)	USA African American, Hispanic, Non-Hispanic, white	
Wright (2012)	Finland Southwestern Finnish	
Bosire (2013)	USA White and Black	
Stott-Miller (2013)	USA Caucasian, African American	
Torfadottir (2013)	Iceland Icelandic population	
Key (2014)	UK Ethnicity NR	
Wilson (2016)	USA White and Black	
Outzen (2016)	Denmark Danish population	
Colorectal Cancer		

Geelen (2007) ***meta-analysis of 19 independent cohort studies***		
Heilbrun (1989)	USA American Japanese	
Hirayama (1990)	Japan Japanese	
Willett (1990)	USA Ethnicity-NR	
Bostick (1994)	USA Mixed: 99%White and Black	
Giovannucci (1994)	USA Ethnicity-NR	
Gaard (1996)	Norway Ethnicity-NR	
Kato (1997)	USA Caucasian, Black, Hispanic, others	
Hsing (1998)	USA White American	
Pietinen (1999)	Finland Southwestern Finnish	
Knekt (1999)	Finland South west, South, Central, North, West, East	
Ma (2001)	USA Ethnicity-NR	
Terry (2001)	Sweden Ethnicity-NR	
Tiemersma (2002)	The Netherlands Western region-Amsterdam Eastern region-Doetinchem Southeastern region- Maastricht	
English (2004)	Australia Australia and other including UK, New Zealand Greece and Italy	
Khan (2004)	Japan Japanese	
Koh (2004)	Singapore Chinese	
Kojima (2004)	Japan Japanese	

Sanjoaquin (2004)	United Kingdom Ethnicity-NR	
Norat (2005)	10 European countries	
Larsson (2005)	Sweden Swedish	
Luchtenborg (2005)	The Netherlands Ethnicity-NR	
Wu (2012) meta-analysis of 41 studies		
Kato (1990)	Japan Ethnicity NR	0.95 (0.63-1.43)
Iscovich (1992)	Argentina Ethnicity NR	
Steinmetz (1993)	South Australia Ethnicity NR	
Kampman (1995)	The Netherlands Western Europeans/Dutch nationality	
Le Marchand (1997)	USA population of Hawaii's five major ethnic groups Japanese, Caucasian, Filipino, Hawaiian	
Fernandez (1999)	Italy Ethnicity NR	
Franceschi (1999)	Italy Southern European	
Tiemersma (2002)	The Netherlands Western region-Amsterdam Eastern region-Doetinchem Southeastern region-Maastricht	
Zhang (2002)	China Chinese	1.52 (0.64-3.59)
Busstra (2003)	The Netherlands Western European origin	
Chiu (2003)	Shanghai China Chinese	Male 1.7 (1.2-2.4) and Female 1.2 (0.8-1.7)
Yang (2003)	Japan Japanese	Male 0.68 (0.47-0.99) Female 0.8 (0.52-1.24)
Kojima (2004)	Japan Japanese	0.95 (0.6-1.51)

Diergaarde (2005)	The Netherlands Caucasian	
Engeset (2007)	Norway Ethnicity NR	
Kimura (2007)	Japan Japanese	0.8 (0.57-1.13)
Hall (2008)	USA Ethnicity NR	
Hu (2008)	Canada Ethnicity NR	
Jedrychowski (2008)	Poland Ethnicity NR	
Ganesh (2009)	India Non-Mumbai Mumbai	0.6 (0.4-0.9)
Lee (2009)	China Chinese	1.3 (0.9-1.9)
Nayak (2009)	India South India population	0.09 (0.03-0.28)
Ramadas (2009)	Malaysia Malay Chinese Indian Others	1.1 (0.42-2.9)
Sugawara (2009)	Northeastern Japan Japanese	0.96 (0.61-1.53)
William (2009)	USA White and African Americans	
Spencer (2010)	UK Ethnicity NR	
Yu (2014) meta-analysis of 20 prospective cohort studies		
Part of the studies are already reported in Wu (2012) above		
Daniel (2011)	USA White and non-Hispanic	
Individual studies reported in the Literature review for fish consumption and colorectal cancer		
Xu (2015)	China Chinese	0.47 (0.36-0.60)

Aglago (2020)	European countries Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom Ethnicity NR	
Lung Cancer		
Song (2014) meta-analysis of 20 studies		
Pierce (1989)	Australia Ethnicity NR	
Marc (1992)	Hawaii Caucasian, Japanese, Chinese, Filipino, and Hawaiian/part-Hawaiian	0.98 (0.62-1.56)
Sankaranarayana (1994)	India South Indian	0.60 (0.24-1.51)
Hugo (1996)	Uruguay Ethnicity NR	
Axelsson (1996)	South west Sweden Scandinavian	
Fredrik (1998)	Sweden Swedish	
Paul (2000)	European countries	
Michael (2001)	USA Ethnicity NR	
Takezaki (2001)	Japan Japanese	0.57 (0.42–0.77)
Kreuzer (2002)	Germany East and West	
Marchand (2002)	France Melanesians, Europeans other ethnic groups mostly Polynesians	
Dosil (2007)	Spain Ethnicity NR	
Shi (2007)	China Chinese	0.35 (0.14-0.83)
Zhang (2007)	China Chinese	0.47 (0.33-0.68)

Hu (2008)	Canada Ethnicity NR	
De Stefani (2009)	Uruguay Ethnicity NR	
Lim (2011)	Singapore Malaysian, Chinese, others	0.47 (0.31-0.73)
Jakob (2011)	European countries Ethnicity NR	
Daniel (2011)	USA White, non-Hispanic	
Takezaki (2003)	Japan Japanese	0.32 (0.13-0.76)
Gastric Cancer		
Wu (2011) meta-analysis of 17 studies		
Buiatti (1991)	Italy Ethnicity NR	
Chen (2002)	USA (Eastern Nebraska) White population	0.58 (0.25-1.40)
Cornée (1995)	France Finnish, Italian and Portuguese	
De Stefani (2004)	Uruguay Montevideo and Other counties	
Fernandez (1999)	Italy (Northern) Italian	
Hamada (2002)	Brazil Japanese Brazilians	
Hoshiyama (1992)	Japan Japanese	0.90 (0.50-1.40
Hu (2008)	Canada Ethnicity NR	
Muñoz (2001)	Venezuela Ethnicity NR	
Phukan (2006)	India (Mizoram) Mizos	0.18 (0.02-5.30)
Pourfarzi (2009)	Iran Iranians	0.37 (0.19-0.70)
Rao (2002)	India Mumbai, Maharashtra and Others	1.4 (0.95-2.00)
Ito (2003)	Japan Japanese	0.60 (0.40-0.90)

Takezaki (2001)	China Chinese	1.35 (0.64-2.85)
Ward (1999)	Mexico Mexican	
Larsson (2006)	Sweden Swedish	
Ngoan (2002)	Japan Japanese	0.90 (0.30-2.10)
Yu (2014) meta-analysis of 20 cohort studies with only 7 cohort studies on gastric cancer		
Part of the studies are already reported in Wu (2011) above		
Nomura (1990)	USA (Hawaii) Japanese American	
Sauvaget (2005)	Japan Japanese	1.16 (0.97-1.39)
Tokui (2005)	Japan Japanese	0.95 (0.68-1.33)
Fish Consumption and Diabetes		
Xun (2012) meta-analysis of 9 prospective cohort studies		
Montonen (2005)	Finland Finnish	
Kaushik (2009)	USA White and Black	
Patel (2009)	UK Ethnicity NR	
van Woudenbergh (2009)	The Netherlands Dutch citizen	
Djoussé (2011)	USA White and Black	
Nanri (2011)	Japan Japanese	0.59 (0.18-1.96)
Villegas (2011)	China Chinese	0.77 (0.63-0.94)
He (Unpublished)	USA Ethnicity NR	
Wallin (2012) meta-analysis of 16 prospective cohort studies		
Vang (2008)	USA	

	Non-Hispanic white	
Brostow (2011)	China Singapore Chinese	1.06 (0.91–1.23)
Meyer (2001)	USA Ethnicity NR	
Hodge (2007)	Australia United Kingdom, Italy, Greece	
Kröger (2011)	Germany Ethnicity NR	
Wu (2012b) meta-analysis of 16 cohort studies		
Wang (2003)	USA Ethnicity NR	
van Dam (2002)	USA White and Black American	
Krachler (2008)	Northern Sweden Swedish	
Zheng (2012) meta-analysis of 24 cohort studies		
Schulze (2003)	USA Ethnicity NR	
Patel (2012)	Europe Netherlands, Sweden Denmark, Germany	
Zhang (2013) meta-analysis of 11 prospective cohort studies		
The studies mentioned in Zhang (2013) are already reported in Xun (2012) above		
Namazi (2019) meta-analysis of 7 prospective cohort studies		
Wallin (2017)	Sweden Swedish	
Rylander (2014)	Norway Norwegian	
Fish Consumption and Mental Health		
Sachez-Villegas (2007)	Spain Spanish	
Depression		
Li (2016) meta-analysis of 26 observational studies		

Tanskanen (2001)	Finland Finnish	
Hakkarainen (2004)	Finland Finnish	
Timonen (2004)	Finland Finnish	
Barberger-Gateau (2005)	France Ethnicity NR	
Sanchez-Villegas (2009)	Spain Spanish	
Colangelo (2009)	USA Ethnicity NR	
Murakami (2010)	Japan Japanese	OR 0.73 (0.55-0.97)
Suominen-Taipale (2010)	Finland Finnish	
Li (2011)	USA Ethnicity NR	
Lucas (2011)	USA Ethnicity NR	
Chrysohoou (2011)	Greece Ethnicity NR	
Albanese (2012)	Cuba, Dominican Republic, Venezuela, Peru, Mexico, China, and India	
Tsai (2012)	Taiwan Taiwanese	
Smith (2014)	Australia Australian	
Mihrshahi (2014)	Australia Australian	
Grosso (2016) meta-analysis of 31 observational studies		
Kamphuis (2006)	Netherlands Dutch	
Miyake (2006)	Japan Japanese	OR 0.89 (0.50-1.59)
Appleton (2007a)	United Kingdom Ethnicity NR	
Appleton (2007b)	Northern Ireland France Ethnicity NR	

Sanchez-Villegas (2007)	Spain Spanish	
Astorg (2008)	France Ethnicity NR	
Murakami (2008)	Japan Japanese	Male: OR 0.58 (0.28-1.19) Female: OR 1.46 (0.57-3.76)
Sontrop (2008)	Canada Ethnicity NR	
Golding (2009)	England Ethnicity NR	
Strom (2009)	Denmark Danish	
Bountziouka (2009)	Greece Cyprus	
Kyrozis (2009)	Greece Ethnicity NR	
Murakami (2010)	Japan Japanese	OR 0.73 (0.55-0.97)
Oddy (2011)	Australia Ethnicity NR	
Da Rocha (2012)	Brazil Ethnicity NR	
Kesse-Guyot (2012)	France Ethnicity NR	
Jacka (2012)	Australia Ethnicity NR	
Beydoun (2013)	USA Ethnicity NR	
Daley (2014)	Australia Ethnicity NR	
Beydoun (2015)	USA Ethnicity NR	
Matsuoka (2017)	Japan Japanese	0.44 (0.23-0.84)
Yang (2018a)	Korea Korean	0.52 (0.37-0.74)
Yang (2018b) of 10 prospective cohort studies		
Persons 2014	USA American Indian, Asian, African American, Hispanic White Other	

The remaining nine studies were already reported in Grosso (2016) meta-analysis above		
Sharifan (2017)	Iran Iranian	
Other Psychiatric Illness		
Anxiety Disorder		
Jacka (2013)	Australia Ethnicity NR	
Natacci (2018)	Brazil White, Mixed, Black, Asian Native	
Cognition		
Kim (2013)	USA White and Black	
Kesse-Guyot (2011)	France Ethnicity NR	
Qin (2014)	China Chinese	
Nooyens (2018)	The Netherland Dutch	
Samieri (2018) meta-analysis of 5 prospective cohort studies		
Three-City (3C) study	French White	
Nurses' Health Study (NHS)	USA White	
Women's Health Study (WHS)	USA White	
Chicago Health and Aging Project (CHAP)	USA White	
RushMemory and Aging Project (MAP)	USA White	
Fish Consumption and All-cause Mortality		
Zhao (2016) Meta-analysis 12 prospective cohort studies		
Bell (2014)	USA White Hispanic Black	

	American Indian or Alaska Native Asian or Pacific Islander	
Kappeler (2013)	USA Non-hispanic white Non-hispanic black Mexican American Other	
Lee (2013) *(8 Asian prospective cohort studies)*	Asian: Bangladesh, mainland China, Japan, Korea, and Taiwan	Men 1.05 (0.95-1.16) Women 0.91 (0.85-0.97)
Takata (2013)	China Chinese	0.86 (0.74-1.00)
Olsen (2011)	Denmark Danes	
Yamagishi (2008)	Japan Japanese	0.92 (0.85-1.00)
Ness (2005)	UK White British	
Folsom (2004)	USA Ethnicity NR	
Nagata (2002)	Japan Japanese	0.94 (0.78-1.12) 0.86 (0.70-1.05)
Gillum (2000)	USA white (84.1%), Black	
Albert (1998)	USA Ethnicity NR	
Daviglus (1997)	USA Ethnicity NR	
Wan (2017) Meta-analysis of 23 prospective cohort studies		
Villegas (2015)	USA Ethnicity NR	
Tognon (2011)	Gotherburg Ethnicity NR	
Pocobelli (2010)	USA Ethnicity NR	
Tomasallo (2010)	USA Ethnicity NR	
Trichopoulou (2009)	Greece Ethnicity NR	
Knoops (2006)	Europe Ethnicity NR	

Kelemen (2005)	USA Ethnicity NR	
Yuan (2001)	China Chinese	0.79 (0.69-0.91)
Mann (1997)	UK Ethnicity NR	
Fraser (1997)	USA Ethnicity NR	
Kahn (1984)	USA Ethnicity NR	
Jayedi (2018) Meta-analysis of 10 publications (14 prospective cohort studies)		
Engeset (2015)	European countries Ethnicity NR	
Owen (2016)	Australia Ethnicity-NR	
Bellavia (2017)	Central Sweden Swedish	
Individual studies reported in the Literature review for fish consumption and mortality		
Zhuang (2018)	USA Ethnicity-NR China; Chinese	0.70 (0.59-0.85)
Outzen (2018)	Denmark Danish	
Otsuka (2019)	Japan Japanese	1.20 (0.89-1.63)
Fish Consumption and Incident Dementia		
Wu (2015) Meta-analysis of 6 prospective cohort studies		
Kalmijn (1997)	The Netherlands Ethnicity NR	
Morris (2003)	USA Black 62% and White 38% Americans	
Huang (2005)	USA African Americans	
Schaefer *(*2006)	USA Ethnicity-NR	

Barberger-Gateau (2007)	France Ethnicity-NR	
Devore (2009)	The Netherlands Dutch	
Cao (2016) Meta-analysis of 43 cohort studies (4 studies on fish and dementia)		
The four studies mentioned in Cao (2016) are already reported in Wu (2015) above		
Zhang (2016) Meta-analysis of 21 cohort studies (4 studies on fish and dementia)		
The four studies mentioned in Zhang (2016) are already reported in Wu (2015) above		
Zeng (2017) Meta-analysis of 9 cohort studies		
Robert (2010)	USA White and Black	
Chan (2013)	Hong Kong	0.99 (0.66-1.49)
Osslon (2015)	Sweden Swedish	