Food for thought

The effect of nutrition on dementia and memory decline

Dissertation

zur Erlangung der Doktorgrades (PhD)

der Medizinischen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität

Bonn

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aus

Curitiba, Brazilien

2018

Angefertigt mit der Genehmigung
der Medizinischen Fakultät der Universität Bonn

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Tag der Mündlichen Prüfung: 23. November 2018

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LIST OF ABBREVIATIONS

AA	Arachidonic acid
Aß	Beta-amyloid
AD	Alzheimer's disease dementia and Alzheimer's dementia
ADAM10	A Disintegrin and metalloproteinase domain-containing protein
ADAS-cog	Alzheimer`s Disease Assessment Scale cognitive subscale
ADL	Activities of daily living
AGE	Advanced glycation end-products
AgeCoDe	German Study on Ageing, Cognition and Dementia in Primary Care Patients
AgeQualiDe	Needs, health service use, costs and health-related quality of life in a large sample of oldest-old primary care patients
ALA	Alpha-linolenic acid
APOE	Apolipoprotein
APP	Aß precursor protein
sAPPα	Alpha-secretase-cleaved soluble Aß precursor protein
sAPPβ	Soluble *APP* beta
B1	Thiamine
B2	Riboflavin
B3	Niacin
B5	Pantothenic acid
B6	Pyridoxine
B7	Biotin
B9	Folate
BACE1	β-site *APP* cleaving enzyme 1
BMI	Body Mass Index
BDR	Blessed Dementia Rating scale
C99	99 amino acids
CASMIN	Comparative Analysis of Social Mobility in Industrial Nations
CCI	Charlson comorbidity index
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHD	Coronary Heart Disease

CI	Confidence interval
CNS	Central Nervous System
CSF	Cerebral Spinal Fluid
CVD	Cardiovascular disease
DASH	Dietary Approach to Stop Hypertension
DELCODE	DZNE-Longitudinal Cognitive Impairment and Dementia Study
DHA	Docosahexaenoic acid
DGLA	Dihomo-γ-linolenic acid
DII	Diet Inflammatory Index
DLB	Dementia with Lewy bodies
DLW	Doubly labeled water
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EDTA	Ethylenediaminetetraacetic acid
EGCG	Epigallocatechin-3-galate
EM	Episodic memory
EPA	Eicosapentaenoic acid
FFQ	Food frequency Questionnaire
FTD	Frontotemporal dementia
FU	Follow up
GDS	Global Deterioration Scale
GP	General practitioner
GLA	γ-Linolenic acid
HEI	Healthy Eating Index
HDI	Healthy Diet Indicator
HPLC	High-performance liquid chromatography
HR	Hazard ratio
IBM	International Business Machines Corporation
ICD	International Statistical Classification
IDE	Insulin-degrading enzyme
IL	Interleukin

IU	International units
JM	Joint Modelling
K1	Phylloquinone
K2	Menadione
Kg	Kilogram
LDL	Low density lipoprotein
LA	Linoleic acid
m^2	Squared meter
MCI	Mild cognitive impairment
MedLey	Mediterranean diet for cognitive function and cardiovascular health in the elderly
mg/l	Milligrams per litre
MI	Multiple imputation
MIND	Mediterranean - DASH Intervention for Neurodegenerative Delay diet
µmol/l	Micromol per litre
MR	Mendelian Randomization
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
MUFA	Mono unsaturated fatty acids
n-3	Omega-3 fatty acids
n-6	Omega-6 fatty acids
ng/ml	Nanogram per millilitre
nmol/l	Nanomol per litre
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l´Enseignement en Neurosciences
Ox-LDL	Oxidized- low density lipoprotein
PCA	Principal Component Analysis

PET	Positron Emission Tomography
PFC	Prefrontal cortex
PREDIMED	The Prevención con Dieta Mediterránea trial
PSEN1	Presenilin-1
PSEN2	Presenilin-2
PUFA	Polyunsaturated fatty acids
RBC	Red blood cell
RCT	Randomized Control Trial
ROS	Reactive oxygen species
RRR	Reduced Rank Regression
SAFA	Saturated fatty acid
SCD	Subjective Cognitive Decline
SES	Socioeconomic status
SIDAM	Diagnostic algorithm in the structured interview for the diagnosis of a dementia
SISCO	SIDAM score
SPSS	Statistical Package for the Social Sciences
SSB	Sugar sweetened beverages
T2D	Type 2 Diabetes mellitus
sTfR	Soluble transferrin receptor
TMT	Trial Making Test
TNF-alpha	Tumor necrosis factor alpha
TT	Treelet transform
VDR	Vitamin D receptor
VLDL	Very low density lipoprotein
WHO	World Health Organization

1 INTRODUCTION

The worldwide number of elderly is rising, and simultaneously the number of people with dementia is also increasing (Blennow et al., 2006; Jicha and Carr, 2010). In 2015 approximately 47 million individuals were diagnosed with dementia, and the prevalence of dementia is expected to double every 20 years (Smith and Blumenthal, 2016; Winblad et al., 2016). Furthermore, not only the number of people with dementia is rising, but also the public health costs for dementia are increasing exponentially (Smith and Blumenthal, 2016). In the past 20 years the care of dementia patients has remarkably improved, from research-driven to personalized and multidisciplinary care (Winblad, et al., 2016). Also, many detrimental and protective factors that affect the risk of dementia have been identified through research (Alzheimer's Association, 2016). Currently, no effective treatment of dementia exists (Winblad, et al., 2016). Therefore, there is also a pressing need for disease prevention, starting with the identification and further examination of modifiable risk factors, such as nutrition (Gustafson et al., 2015). Taking this all into account, dementia is a challenging ongoing public health burden on society, which needs targeted research strategies to identify modifiable preventive factors and treatments to delay the onset of the disease or to slow disease progression (Winblad, et al., 2016).

1.1. DEMENTIA

All-cause dementia - Dementia is generally irreversible and characterized by deficits in one or more cognitive domains such as aphasia, apraxia, agnosia, or executive dysfunction (Sahathevan, 2015). In contrast to mild cognitive impairment (MCI), the impairment(s) are present to such an extent that they largely interfere with daily life activities (Alzheimer's Association, 2016). Dementia occurs as a result of damaged or destroyed neurons in parts of the brain involved in cognitive function (Alzheimer's Association, 2016). Alzheimer’s disease (AD) is the most common cause of dementia in individuals aged 60 years and older, thereafter follows vascular dementia or dementia caused by multiple strokes (Morris, 2012). Other kinds of common dementias are frontotemporal dementia (FTD) (i.e. behavioral and speech dysfunction, caused by intraneuronal ubiquitin and tau inclusions), dementia with Lewy bodies (DLB) (i.e. similar

symptoms to AD, sleep disturbances and/or symptoms of Parkinson's disease, caused by abnormal aggregations of the protein Alpha-synuclein in neurons), mixed dementia (i.e. mixed pathologies such as combinations of AD, cerebral infarctions or DLB), Parkinson's disease dementia (i.e. movement problems and similar pathology as AD and DLB due to Alpha-synuclein aggregation in the substantia nigra) (Alzheimer's Association, 2016; Martin and Preedy, 2015; Morris, 2012). Although, generally irreversible, some dementias caused by vitamin deficiencies, brain tumors or chronic alcohol abuse can be reversed when treated at an early stage (Morris, 2012). The diagnosis of dementia is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria, and is either classified under the umbrella of major neurocognitive disorders or mild neurocognitive disorders, depending on the disease stage (American Psychiatric Association, 2013).

Alzheimer's disease dementia (AD) - AD is the primary cause of dementia, accounting for approximately 60-80 % of dementia cases (Alzheimer's Association, 2016). Most AD cases have solely AD pathology, but others may have mixed pathologies such as vascular dementia or DLB as mentioned above (Alzheimer's Association, 2016). In addition, two forms of AD can be distinguished: sporadic and familial AD (Giannopoulos and Pratico, 2015). Sporadic AD is the most common form, and occurs as a result of complex interactions between genetic risk factors and environmental risk factors (Giannopoulos and Pratico, 2015). On the other hand, familial AD, which accounts for an estimated five percent of AD cases, are caused by mutations in single genes that are inherited in an autosomal-dominant manner (Giannopoulos and Pratico, 2015). To date, three genes are known to cause familial forms of AD: 18 mutations in the gene encoding for the amyloid precursor protein (*APP*), and mutations in the genes encoding for presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*) which are part of the y-secretase complex (Papassotiropoulos et al., 2006). Individuals who inherit a mutation to the *PSEN2* gene have a 95 % risk of developing AD (Alzheimer's Association, 2016; Goldman et al., 2011).

One of the earliest symptoms of AD is a slowly worsening ability to remember new information, due to neurological damaging in, for example, the medial temporal lobe (MTL) including the hippocampus (Alzheimer's Association, 2016). A slow decline in

episodic memory (EM) is already present in the preclinical stage of AD (Small et al., 2003). As the disease progresses it becomes more difficult for the individual to learn new information, these difficulties can also be observed in cognitive tests such as the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word list (Giannopoulos and Pratico, 2015; Morris et al., 1989). Furthermore, language decline in speaking and writing occurs simultaneously with the loss of 'function words' and increasing use of 'passe-partout' words (Giannopoulos and Pratico, 2015). Other examples of common symptoms are: difficulties in planning or problem solving, difficulties with household chores or familiar tasks at leisure, depression, apathy, anxiety, sleep problems, and isolation (Alzheimer's Association, 2016). According to the most recent AD diagnostic criteria, AD can be diagnosed solely based on evidence of biomarkers, i.e. also in the absence of manifest clinical symptoms (i.e. preclinical AD) (Jack et al., 2018), whereas earlier criteria required memory loss and a decline in thinking abilities for an AD diagnosis to be made (Alzheimer's Association, 2016). It has been hypothesized that the accumulation of abnormally protein beta-amyloid ((Aβ) plaques) and the accumulation of an abnormal form of the protein tau (tau tangles) are two key brain changes that might contribute to the damage of neurons causing the aforementioned symptoms of AD (Alzheimer's Association, 2016; Scheltens et al., 2016). This hypothesis comes from studies that examined familial AD and involves the mutations in *APP*, *PSEN1*, or *PSEN2* (Karch and Goate, 2015).

The accumulation of Aβ plaques, which takes place outside neurons, is a result of the amyloidogenic pathway where *APP* cleaves to β-secretase (β-site APP cleaving enzyme 1; *BACE1*), which leads to the release of s*APP*β and saves 99 amino acids (C99) of APP (Giannopoulos and Pratico, 2015). Consequently, the C99 fragments are cleaved by y-secretase (*PSEN1, PSEN2*), which releases two important isoforms of Aβ: $A\beta_{1-40}$ and $A\beta_{1-42}$ (Giannopoulos and Pratico, 2015). The neurotoxic $A\beta_{1-42}$ oligomerize and form Aβ plaques, whereas $A\beta_{1-40}$ is less likely to be neurotoxic and to aggregate (Giannopoulos and Pratico, 2015). The Aβ plaques disturb the communication between neurons, which in turn results into cell death (Alzheimer's Association, 2016). Furthermore, in AD neurofibrillary tangles are formed, which contain hyperphosphorylated and aggregated forms of tau protein (Giannopoulos and Pratico, 2015; Iqbal et al., 2005). Hyperphosphorylated tau, present within neurons, is

characterized by insolubility, to be detached from microtubules and to form into paired helical filament structures, which in turn form neurofibrillary tangles (Giannopoulos and Pratico, 2015). Within neurons tau tangles block the transport of essential nutrients and molecules, consequently leading to cell death (Alzheimer's Association, 2016). Interestingly, mutations in the tau gene are involved in the development of frontotemporal dementia without Aβ plaques, whereas in AD both function as synergists (Scheltens, et al., 2016).

1.2. COGNITIVE DECLINE

As we age we experience a natural decline in cognitive ability, such as, memory and language impairments, loss of visuospatial awareness and a decrease of concentration (DeCarli, 2003). In the past two decades several definitions of cognitive impairment have been established, including ageing-associated cognitive decline (Levy, 1994), and MCI (DeCarli, 2003; Graham et al., 1997). In contrast to individuals with ageing-associated cognitive decline, individuals with MCI are at high risk for all-cause dementia or AD.

Mild cognitive impairment - The syndrome of MCI has been introduced by Reisberg et al. (1988) (Reisberg et al., 1988) and was later adopted by Petersen et al. (1997) who defined the concept as “a transitional stage between normal aging and probable AD”. Individuals with MCI have a cognitive test score below the normal range for their age and education, have deficits in at least one cognitive domain, and are still able to function normally to a large extend, i.e. are not sufficiently impaired to constitute dementia (Albert et al., 2011; Bondi and Smith, 2014). The syndrome has a heterogeneous concept, it can be amnestic (i.e. clinically significant memory impairment), non-amnestic (i.e. affecting non-memory related cognitive domains), single domain or involving multiple cognitive domains (Winblad et al., 2004). In addition, it has been reported that some individuals will progress to AD or other forms of dementia, some remain stable and others recover (Winblad, et al., 2004). Observational studies have reported that older age (>85 years), presence of Apolipoprotein ε4 (*APOE* ε4) allele, history of stroke and subjective memory complaint, as potential risk factors for MCI (Etgen, 2015). However, individuals with a higher level of cognitive impairment tend

to show a more rapid cognitive decline as compared to individuals who are less impaired (Etgen, 2015).

1.3. MEMORY DECLINE

Long-term memory - Long-term memory can be categorized into: explicit (declarative) memory, which requires the conscious recall of stored information, and implicit (non-declarative) memory, which is based on learning (Tromp et al., 2015). Declarative memory is categorized into semantic memory and EM (Tromp, et al., 2015). Semantic memory is related to general information storage, and EM is a 'cognitive system' which records (or encodes), stores, and retrieves information about the individuals experiences and the temporality and spatial contexts of those experiences (Tromp, et al., 2015).

Episodic memory - Within EM three processes can be distinguished: encoding, consolidation and retrieval (Tromp, et al., 2015). Encoding is considered as the first stage of EM, it takes place in the prefrontal cortex (PFC) and MTL (Tromp, et al., 2015). This stage is important for the storage of voluntary information, obtained from external stimuli, and for its retrieval (Tromp, et al., 2015). Consolidation takes place in the hippocampus and neocortex, its purpose is to maintain and reorganize memories into long-term memory (Tromp, et al., 2015). Additionally, retrieval, which takes place in the MTL, medial and lateral prefrontal cortices, angular gyrus, retrospenial cortex and posterior cingulated cortex, is meant for the individual to reactivate stored information (Tromp, et al., 2015; Tulving, 1983).

Furthermore, EM can be categorized into nine properties (Conway, 2009). At first, EM can be defined as a "summary record of experiences". The second property relates to the first one, the memories are aimed to keep a specified record of aspects of experiences that might be relevant to future goals, depending on the need of the memory the experience will be activated or inhibited. Properties three, four and five represent the nature of EM, which includes visual EM, the perspective of the visual EM (i.e. field: how the individual sees him or herself in the memory, either as an observer or from the original perspective) and 'snapshots' of the experience. Furthermore, property six represents the temporal dimension of the memories in order of occurrence and

property seven indicates that EM do not endure for long periods of time. Lastly, EM provides memory specificity (i.e. only a small percentage of EM are being kept in long term memory, because they might be of use for future goals) and they initiate recollective experience (Conway, 2009). In older age, neurons and neurotransmitters decrease (i.e. numbers and size), and synaptic contacts lose their efficiency primarily in the frontal brain regions (Tromp, et al., 2015). EM is highly affected by aging and AD in particular, mainly due to brain atrophy in the PFC and hippocampal volume shrinkage (Kramer et al., 2005; Tromp, et al., 2015). Also, the temporal hippocampal system, parietal cortex, cerebellum, thalamus and the cingulate gyrus are of great importance to control and organize the encoding and retrieval of EM (Tromp, et al., 2015).

1.4. RISK FACTORS FOR DEMENTIA

Dementia, at least in its most common sporadic forms, is a result of multiple factors. Therefore, research has focused on the identification of risk factors to prevent or detect the disease at an earlier stage are critical (Alzheimer's Association, 2016). Thus far, aging, carrying the *APOE* ε4 gene and, for AD in particular, a family history of AD have been identified as main non-modifiable risk factors (Alzheimer's Association, 2016). In addition, modifiable cardiometabolic health risk factors have been identified such as hypertension, diabetes mellitus (DM), high cholesterol, obesity, physical activity, and smoking (Alzheimer's Association, 2016). Furthermore depression and lower education may also increase risk for dementia (Alzheimer's Association, 2016; Byers and Yaffe, 2011).

Ageing - As age increases a gradual decline in cognitive function is expected, however, this cognitive decline may or may not result in a dementia (Sahathevan, 2015). In fact, some elderly are able to live out their lives without cognitive impairments. Hebert et al. (2013) predicts that in the United States alone 13.8 million people will develop AD in 2050 and only seven million of the total will be aged 85 years or older.

Apolipoprotein - The main genetic risk factor for familial and sporadic AD which contributes to the pathogenesis of the disease is *APOE*; *APOE* ε4 to be precise (Alzheimer's Association, 2016). *APOE* consists of three isomers: E2, E3 and E4, which

in turn are coded as ε2 ε3 ε4 alleles on chromosome 19 (Sahathevan, 2015; Utermann, 1987). The ε3 allele is the most frequently inherited allele, and ε2 is the least frequent (Alzheimer's Association, 2016). Individuals with the ε4 allele have a greater risk of developing AD (Alzheimer's Association, 2016). In the bloodstream the *APOE* gene plays a role in the transportation of cholesterol (Sahathevan, 2015). Additionally, in the brain *APOE* is expressed by non-neuronal cells (e.g. astrocytes and microglia), where *APOE* functions as a binder of high density-like lipoprotein particles, in particular during receptor-mediated endocytosis (Kim et al., 2009). It has been hypothesized that the interaction between *APOE* and Aβ contributes to AD pathogenesis, as *APOE* may function as an Aβ-binding protein (Kim, et al., 2009). Also, *APOE* ε4 might contribute to a gain in toxic function, a loss of protective function or maybe both (Kim, et al., 2009)

Family history of AD - In comparison to individuals without first-degree relatives who developed AD, individuals with at least one first-degree relative with dementia have a two to four fold risk of developing AD (Lautenschlager et al., 1996). Individuals with an identical twin with AD are at the highest risk for the disease (Gatz et al., 2006). However, these risks might be influenced by age and uncertainty of the diagnosis of AD in family members with chronic diseases or the inability to classify family members who died prior to the age of risk (Jarvik et al., 2008). Furthermore, the risk to develop AD due to family history may diminish with age and may be minimal or absent after the age of 85 years (Jarvik, et al., 2008; Silverman et al., 2003).

Hypertension - Hypertension may lead to changes in the brain that contribute to the development of dementia (Launer et al., 2000). It might affect the autoregulation of blood flow to the brain (Launer, et al., 2000), or cause microangiopathy, which causes lipohyalinos and fibrinoid necrosis that lead to thrombotic occlusion of the lumen, and damage the walls of cerebral microvessels (Roman et al., 2002). These brain changes increase the risk of subcortical lacunar infarction and chronic ischemia, which in turn are risk factors for the development of dementia (Roman, et al., 2002; Sahathevan, 2015).

Diabetes Mellitus - It has been postulated that DM contributes to dementia through its effect on vascular mechanisms, toxic effects of hyperglycemia or due to insulin resistance (Gudala et al., 2013). Furthermore, hyperinsulinemia might inhibit catabolization of Aβ by insulin-degrading enzyme (IDE) and hyperglycemia may

contribute to neuritic plaque and neurofibrillary tangles formation through advanced glycation end-products (AGE) (Gudala, et al., 2013; Sahathevan, 2015). In addition, AGE might also play a role in microtubule associated tau protein stabilization and the formation of tau tangles (Gudala, et al., 2013).

Obesity - The association between obesity and the risk of dementia might vary with age (Ronnemaa et al., 2011). Mid-life obesity has been associated with higher dementia risk, whereas late-life obesity has been associated with a lower dementia risk (Fitzpatrick et al., 2009; Hughes et al., 2009). However, one study observed a J-shape association between Body Mass Index (BMI) and dementia, and reported an increased risk of dementia in participants with a BMI less than 20 and above 22 (Rosengren et al., 2005). Another study including two million participants reported a protective effect of high BMI in mid-life and late-life (Qizilbash et al., 2015). Several factors such as diet, physical activity, frailty or weight change might explain the association (Qizilbash, et al., 2015). High late-life BMI might be protective as it contributes to, for example, high late-life cholesterol, glucose and leptin levels, which in turn have been proven to be protective against dementia risk (Emmerzaal et al., 2015).

Smoking - The relationship between smoking with the different kinds of dementias and the underlying mechanisms still needs to be elucidated (Beydoun et al., 2014). Studies have reported mixed results (Beydoun, et al., 2014). However, it is clear that smoking increases the risk of stroke (Gorelick et al., 1999), which in turn is a risk factor for vascular dementia. Furthermore, it has been hypothesized that smoking contributes to oxidative stress and inflammation; two well-known pathways leading to the development of dementia (Beydoun, et al., 2014).

Physical activity - Growing evidence suggests that physical activity has a protective effect on dementia (Blondell et al., 2014; Harrington et al., 2016). Physical activity enhances blood flow to the brain, which provides brain cells with oxygen and nutrients (Sofi et al., 2011). Furthermore, physical activity contributes to the formation of synapses, neuronal cell growth and survival (Sofi, et al., 2011). Also, an active lifestyle decreases the risk for DM, hypertension or dyslipidemia, which in turn are risk factors for dementia (Sofi, et al., 2011).

High cholesterol - As mentioned previously, high mid-life cholesterol may be a risk factor for dementia, whereas high late-life cholesterol may have a protective role (Emmerzaal, et al., 2015). In the brain, cholesterol is formed from *de novo* biosynthesis, as it is not possible for very low density lipoproteins (VLDL) and low density lipoproteins (LDL) to cross the blood-brain-barrier (Di Paolo and Kim, 2011). Cholesterol regulates secretase enzymes, intervenes with Aβ transportation, stimulates Aβ aggregation and modulates the neurotoxicity of Aβ plaques (Di Paolo and Kim, 2011; Sahathevan, 2015).

Depression - Depression can commence across the life course, whereas dementia generally starts in late life (Byers and Yaffe, 2011). Studies have found an association between depression and dementia, however, the timing of depression is key to defining the nature of the association (Byers and Yaffe, 2011). In fact, a two-fold or greater increase in risk of dementia has been observed for earlier-life depression or depressive symptoms (Byers and Yaffe, 2011). On the other hand, associations have been observed between late-life depression and dementia (Byers and Yaffe, 2011). However, it remains unknown if late-life depression is a prodrome, consequence or a risk factor for dementia (Byers and Yaffe, 2011). Several postulated mechanisms linking depression to dementia have been hypothesized (e.g. cardiovascular diseases; CVD) (Byers and Yaffe, 2011).

Education - Higher level of education might have a protective effect on the development of dementia (Alzheimer's Association, 2016). This hypothesis is also known as “cognitive reserve”, which suggests that more connections between neurons are established, which enables the brain to use other routes of neuron-to-neuron communication during early dementia onset (Alzheimer's Association, 2016). However, it could also be that individuals with fewer years of education tend to obtain jobs that are on the one hand less mentally stimulating (i.e. offering less chance to build up cognitive reserve during mid-life) but also are associated with a lower socioeconomic status (SES), which in turn might have caused an unhealthy lifestyle or inability to afford health care for cardiovascular risk factors (Alzheimer's Association, 2016).

1.5. PATHWAYS LEADING TO DEMENTIA

Nutritional factors, for example, vitamins or fatty acids have been hypothesized to protect against oxidative stress and inflammation, two pathways which contribute to the development of dementia. An outline on these pathways will be given in the following.

Oxidative stress - Oxidative stress is an imbalance between antioxidant capacity and reactive oxygen species (ROS) (MacNee, 2000; Melo van Lent et al., 2016; Schunemann et al., 2001), it is one of the causal pathways leading to risk factors of dementia (e.g. CVD) and it is one of the pathogenic mechanisms in AD or all-cause dementia (Loef and Walach, 2012; Pope et al., 2003). The role of antioxidants (e.g. vitamin E) is to fight against ROS, which can be divided into exogeneous oxidants (e.g. cigarette smoke) and endogeneous oxidants (i.e. formed by inflammatory cells) (Genestra, 2007; Halliwell, 1990; Melo van Lent, et al., 2016). Oxidative stress may lead to an increased demand of antioxidants, consequently decreasing their circulating concentrations (Lopes da Silva et al., 2014). In the brain neuronal membranes are vulnerable to lipid peroxidation (i.e. an indicator of free radical activity and reflects damage to membranes and probably other organelles or deoxyribonucleic acid (DNA) (Gropper et al., 2009)) caused by oxidative stress, because of their high content of polyunsaturated fatty acids (PUFAs) (Lopes da Silva, et al., 2014). Vitamins with antioxidant capacities (e.g. vitamin E) and the mineral selenium aim to counteract this process by protecting the lipid precursors and the neuronal membrane components (Lopes da Silva, et al., 2014). Furthermore, oxidative stress in the brain contributes to neuronal death due to Aβ aggregation, and changes in tau protein (Solfrizzi et al., 2011). Also, in these processes nutritional factors have been suggested to play a role in repairing or preventing damages (Lopes da Silva, et al., 2014).

Inflammation - Inflammation is a second pathway caused by an imbalance between anti-inflammatory capacity and pro-inflammatory cytokines or compounds (e.g. interleukin; IL-1 b, IL-6 and tumor necrosis factor; TNF-alpha), which is one of the causal pathways leading to dementia (Holmes, 2013). In this pathway, microglia cells, which have a neuroprotective role in AD, are thought to secrete proteolytic enzymes that act against Aß, (Shudo et al., 2009). However, it has been demonstrated in a mouse model

that deficiency of chemokine receptors such as c-c-receptor type 2 impairs microglial accumulation and accelerates the progression of AD-like diseases (Shudo, et al., 2009). Furthermore, chronic inflammation and astrocytosis promote astrocytes and microglia to produce cytokines in response to Aß induced injury, consequently contributing to an increase in plaque formation (Shudo, et al., 2009). Vitamins with anti-inflammatory properties such as vitamin A, tend to act against the production of cytokines such as IL-6 and TNF-alpha and microglial activation (Shudo, et al., 2009).

1.7. THE ROLE OF NUTRITION IN COGNITIVE HEALTH

Nutrition is an important modifiable lifestyle factor throughout the lifespan. It has an impact on a wide range of diseases including CVD and DM (Archundia Herrera et al., 2017), which in turn are risk factors for dementia (Alzheimer's Association, 2016). A growing body of evidence points to an important role of nutrition in the development of dementia and its progression rate (Gustafson, et al., 2015). To the present, research groups have examined specific nutrients (e.g. vitamin C), nutrient groups (saturated fatty acids; SAFA), individual foods (e.g. butter), food groups (e.g. green leafy vegetables), and dietary patterns (e.g. Mediterranean diet)) in relation to cognitive health outcomes. In this section an overview will be given on the current state of knowledge.

1.7.1. NUTRIENTS

The evaluation of individual nutrients in relation to AD or dementia has received great interest (Gustafson, et al., 2015). Lopes da Silva et al. (2014) conducted a systematic review and meta-analyses to investigate the presence of different plasma nutrient concentrations between AD patients and healthy controls. The authors reported that concentrations of vitamins (A, B12, C, D and E), folate and zinc were lower in AD patients as compared to healthy controls (Gustafson, et al., 2015; Lopes da Silva, et al., 2014). In addition, lower concentrations of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and total omega-3 (n-3) PUFAs were found in patients with all-cause dementia as compared to healthy controls (Gustafson, et al., 2015; Lin et al., 2012). According to the above, nutrition research should not only focus on single foods, but also examine nutrients as these “small” compounds might have an impact on a greater scale.

VITAMINS

Vitamins are essential nutritional compounds that can be acquired from the diet only (Gropper, et al., 2009). They can be categorized into water-soluble vitamins and fat-soluble vitamins (Gropper, et al., 2009). The current state of knowledge will be outlined in the following section.

WATER-SOLUBLE VITAMINS

B vitamins - the group of B vitamins consist of eight water-soluble vitamins: thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9), and vitamin B12. The vitamins can be found in animal products (e.g. steak, pork, chicken, fish, eggs and milk), vegetables (e.g. spinach, asparagus and mushrooms), seeds, legumes, beans, yeast, whole grains and potatoes (Gropper, et al., 2009). B vitamins function as coenzymes to contribute to the regulation of cellular functioning such as energy metabolism, and the synthesis of bioactive molecules such as amino acids and fatty acids (Kennedy, 2016). Furthermore, the vitamins contribute to two related cellular processes: the “folate cycle” and the “methionine cycle” (Kennedy, 2016). In the folate cycle dietary tetrahydrofolate (one active form of folate) cycles through multiple enzymatic modifications, to produce one-carbon units for one carbon metabolism (i.e. the creation of amino acids, purines or methyl groups) (Kennedy, 2016). In addition, in the methionine cycle the amino acids methionine and homocysteine are interconverted and result into methyl groups, which in turn are needed for genomic and non-genomic methylation reactions (Kennedy, 2016). Furthermore, the vitamins play significant roles in the brain. The vitamins contribute to the synthesis of compounds which are precursors to neurotransmitters, the metabolism of essential fatty acids in brain lipids, the fight against oxidative stress and inflammation, the formation and function of brain cells, brain glucose regulation, neuronal differentiation, and the protection of cell membrane phospholipids (Kennedy, 2016). Although all eight B-vitamins have a significant value for cognitive health, only vitamin B6, folate and vitamin B12 have been examined in relation to cognitive health outcomes (Kennedy, 2016). A large review (2008) including 84 cross-sectional studies and 25 longitudinal studies reported that 77 (n= 34,000) out of 84 cross-sectional studies demonstrated that low concentrations of vitamin B6, folate and vitamin B12 were associated with worse cognitive test performance (Smith, 2008). In addition, lower concentrations or intake of

vitamin B6, folate and vitamin B12 were associated with an increased rate of cognitive decline or incidence of AD (Smith, 2008). Similar results have been observed in two more recent systematic reviews (Michelakos et al., 2013; O'Leary et al., 2012). By contrast, a systematic review and meta-analysis (2013) including eight longitudinal studies (n= 5,254) reported no association between higher vitamin B12 intake and incident all-cause dementia, incident AD or global cognition (Doets et al., 2013). Also, meta-analyses of Randomized Control Trials (RCTs) (2012, 2014) including 19 or 11 studies have reported no association between folic acid, B12 and/or B6 supplementation and better cognitive performance or slower cognitive decline (Clarke et al., 2014; Ford and Almeida, 2012).

Vitamin C - is a water-soluble vitamin which is known as ascorbic acid or ascorbate (Gropper, et al., 2009). Foods rich in vitamin C are fruits (e.g. oranges) and vegetables (e.g. broccoli) (Gropper, et al., 2009). Vitamin C is important for neurotransmitter synthesis and contains anti-oxidative properties to fight against oxidative stress, including lipid peroxidation (Gropper, et al., 2009). To present, higher vitamin C intake (n= 33,252), plasma concentrations (n= 1,951) and measured in Cerebral Spinal Fluid (CSF) (n= 32) has been associated with better cognitive function, lower odds of cognitive impairment or AD, slower cognitive decline or a reduced risk of AD (Bowman, 2012; Kalli, 2017). Travica et al. (2017) conducted a systematic review including 5 RCTs. One RCT found that cognitively normal individuals who received vitamin C supplementation had a better cognitive test performance as compared to the control group, but one RCT found no significant differences between the vitamin C supplement group and the control group (Travica et al., 2017). In addition, two of three RCTs reported that vitamin C supplementation did not improve cognitive test performance in cognitively impaired (including AD) individuals, and one RCT found no association at all (Travica, et al., 2017).

FAT-SOLUBLE VITAMINS

Vitamin A and beta-carotene - vitamin A is a vitamin which consists of a group of compounds including: retinol, retinal, and retinoic acid (Gropper, et al., 2009). Vitamin A can be found in, for example, liver, dairy products and fish (Gropper, et al., 2009). In addition, Provitamin A carotenoids consist of >600 carotenoids, but less than 60

carotenoids – including beta-carotene – can actually convert into vitamin A (Gropper, et al., 2009). One source of provitamins A are fruits and vegetables, of which carrots are an important source of beta-carotene (Gropper, et al., 2009). Vitamin A contributes to the formation of the Central Nervous System (CNS) and regulates genes that are expressed in the CNS (Gropper, et al., 2009). In fact, it has been suggested that vitamin A regulates *APP, BACE1, PSEN1, PSEN 2*, A Disintegrin and metalloproteinase domain-containing protein 10 (*ADAM10*) and *APOE*, which are all involved in the development of AD (Sauvant et al., 2015). Furthermore, vitamin A and beta-carotene have antioxidant properties, which are needed to act against oxidative stress in the brain (Gropper, et al., 2009). Beta-carotene primarily tends to act against lipid peroxidation (Gropper, et al., 2009). In addition, animal and cell studies have demonstrated that vitamin A and beta-carotene inhibit the formation of Aß fibrils and the aggregation of $Aß_{40}$ and $Aß_{42}$, consequently protecting the brain against plaque formation (Ono and Yamada, 2012; Sauvant, et al., 2015). Despite the implicated roles of vitamin A and beta-carotene, epidemiological evidence is inconclusive. Small case-control studies found significantly lower concentrations of vitamin A in AD or all-cause dementia patients as compared to controls (Foy et al., 1999; Jimenez-Jimenez et al., 1999; Lopes da Silva, et al., 2014; Polidori and Mecocci, 2002; Raszewski et al., 2016; Rinaldi et al., 2003), but others did not (Lopes da Silva, et al., 2014). In addition, observational studies (range: n= 298-1,769) found no association between concentrations of vitamin A with global cognition or cognitive decline (Johnson et al., 2013; Kang and Grodstein, 2008; Schmidt et al., 1998). Heterogeneous results have also been reported for concentrations of beta-carotene. One longitudinal study (n= 455) and two cross-sectional studies (n= 81 and n= 232) reported significant associations with cognitive decline and all-cause dementia or AD (Hu et al., 2006; Jimenez-Jimenez, et al., 1999; von Arnim et al., 2012). By contrast, one longitudinal study (n= 858) and six cross-sectional studies (range: n= 58-1,769) did not find an association with global cognition, cognitive decline or AD (Foy, et al., 1999; Johnson, et al., 2013; Kang and Grodstein, 2008; Polidori and Mecocci, 2002; Rinaldi, et al., 2003; Schippling et al., 2000; Schmidt, et al., 1998). No RCTs have yet been carried out to examine the relationship between vitamin A or beta-carotene and cognitive health outcomes.

Vitamin D - vitamin D can be obtained from sun exposure (i.e. previtamin D_3 or precalciferol) or through diet (Gropper, et al., 2009). Two forms of vitamin D through diet exist: previtamin D_2 or ergosterol from plants, and vitamin D_2 or ercalciferol sold commercially (Gropper, et al., 2009). Foods containing vitamin D are mainly animal products (e.g. liver, eggs, dairy products and fish) (Gropper, et al., 2009). At the end of the life course, vitamin D intake decreases due to reduced sunlight exposure, reduced fat intake and absorption, and conversion into vitamin 1,25-$[OH]_2$ D_3 (i.e. active form of vitamin D) (Watson et al., 2018). Vitamin D (i.e. 1,25-$[OH]_2$ D_3) conducts its roles through two mechanisms: as a steroid hormone or as a promotor for genomic actions, which contributes to gene transcription (Gropper, et al., 2009). The vitamin is involved in several brain functions for example: scavenging oxidative stress, regulating cytokines in the inflammation pathway, contributing to the release of neurotransmitters, and acting against Aß aggregation (Gezen-Ak et al., 2014; Landel et al., 2016; Sommer et al., 2017). The vitamin D receptor (VDR), which functions as a gene regulator, has been found in several areas of the brain: the cortex, hippocampus, dopamine neurons and in the brain nucleus (Brouwer-Brolsma and de Groot, 2015; Cui et al., 2013; Eyles et al., 2014; McCann and Ames, 2008). It has been found that Aß is able to obstruct the use of vitamin D, causing “inefficient utilization of vitamin D”, consequently vitamin D deficiency may induce an accumulation of Aß due to an inbalance of calcium homeostasis, or increased oxidative stress (Gezen-Ak, et al., 2014). An umbrella review (2015) reported that four systematic reviews including meta-analyses have demonstrated an association between lower concentrations of vitamin D and worse executive function, global cognitive function or risk of cognitive impairment, however, one systematic review reported no effect of vitamin D on cognitive function (Krause and Roupas, 2015). A second systematic review and meta-analysis including 18,974 individuals also demonstrated that vitamin D deficiency was associated with an increased risk of incident AD (Sommer, et al., 2017). However, three recent longitudinal studies (2014, 2017) (range: n= 1,182-1,663) did not find any association between low concentrations of vitamin D and risk of incident all-cause dementia or AD (Karakis et al., 2016; Olsson et al., 2017; Schneider et al., 2014). To date, a limited number of RCTs have been carried out to investigate the role of vitamin D in cognitive health (Landel, et al., 2016). A two phase intervention (n= 18) (Landel, et al., 2016; Stein et al., 2011) reported that

participants who received 3000 International Units (IU) of vitamin D supplementation had a better Alzheimer`s Disease Assessment Scale-cog (ADAS-cog) test performance, but in the second phase the effect was not observed for ADAS-cog in participants who received 1000 or 6000 IU of vitamin D supplementation (Landel, et al., 2016; Stein, et al., 2011). In addition, a pilot study (n= 43) demonstrated that individuals who received vitamin D and memantine (i.e. contributes to the maintenance of memory) had a superior cognitive test performance as compared to individuals who received vitamin D or memantine only (Annweiler et al., 2012; Landel, et al., 2016).

Vitamin E - vitamin E consists of two groups, the tocopherols (i.e. alpha-tocopherol, beta-tocopherol, gamma-tocopherol, and delta-tocopherol) and the tocotrienols (i.e. alpha-tocotrienols, beta-tocotrienols, gamma-tocotrienols, and delta-tocotrienols) (Gropper, et al., 2009). Alpha-tocopherol is of particular interest as it is the only biologically active form (Gropper, et al., 2009), on the other hand it has been demonstrated that tocotrienols have stronger antioxidant properties (Galli et al., 2007; Nesaretnam, 2008). Vitamin E can be found in plant based and animal based foods including vegetable oils (e.g. canola oil, olive oil and sunflower oil), wheat germ, soybean, margarine, nuts, eggs, meat, fish, fruits and vegetables (Gropper, et al., 2009). In the brain, vitamin E is of particular interest because it may function as a neuroprotector and may fight against Aß free radicals (Hu et al., 2013; Lin and Beal, 2006) Furthermore, vitamin E contributes to the regulation of inflammatory response, promotes cellular signaling, counteracts cell proliferation, and is involved in gene expression (i.e. genes related to oxidative stress, cholesterol homeostasis, inflammatory pathways, transportation of cells, and the release of neurotransmitters) (Boccardi et al., 2016). To date, no systematic review has been conducted on the association between vitamin E and cognitive health outcomes. Boccardi et al. (2016) wrote a review in which ten observational studies were discussed. A large longitudinal study (n= 5,395) showed an association between higher vitamin E intake (alpha-tocopherol) with a decreased risk of incident AD (Boccardi, et al., 2016). A second longitudinal study (n= 4,809) also observed an association between low concentrations of alpha-tocopherol and worse memory (Boccardi, et al., 2016). In addition, observational studies (range: n= 16-1,033) demonstrated that concentrations or dietary intake of vitamin E (alpha-tocopherol) were related to cognitive function, AD or cognitive impairment (Boccardi, et al., 2016).

However, four longitudinal studies reported that concentrations of total tocopherols and total tocotrienols, rather than concentrations of alpha-tocopherol alone, were associated with cognitive decline or AD (Boccardi, et al., 2016). RCTs investigating vitamin E have also reported conflicting results. A Cochrane review of RCTs in an AD or MCI study population demonstrated a slowing functional decline in AD patients after receiving 2000 IU/d of vitamin E (alpha-tocopherol) over 2.27 years of follow up (Farina et al., 2017). A second RCT reported lower and higher levels of oxidative stress in AD patients after 800 IU of vitamin E supplementation (Farina, et al., 2017). However, two RCTs did not observe a significant difference in cognitive test performance between AD or MCI participants who received vitamin E supplementation and the control group (Farina, et al., 2017).

Vitamin K - vitamin K is also known as phylloquinone (K1) or menadione (K2) (Grimm et al., 2016; Gropper, et al., 2009). Vitamin K1 is abundantly present in green leafy vegetables (e.g. kale) (Grimm, et al., 2016; Gropper, et al., 2009). Other sources of vitamin K1 are other vegetables, fruits (e.g. kiwi), legumes, beans, peanut butter, and coffee (Grimm, et al., 2016; Gropper, et al., 2009). On the other hand, vitamin K2 can be found in poultry, eggs and butter (Grimm, et al., 2016). The vitamin plays a role in blood clotting, bone mineralization and arterial calcification (Gropper, et al., 2009). Furthemore, vitamin K is important in the CNS and in the brain where it functions as a neuroprotector (Grimm, et al., 2016). As compared to the other fat-soluble vitamins, vitamin K is not widely studied with regard to cognitive health outcomes. A recent review (2017) sumarized the limited evidence of the relation between vitamin K and cognitive impairment or AD (Fenech, 2017). The author reported that four cross-sectional studies (range: n= 62–160) demonstrated an association between low vitamin K intake or vitamin K deficiency with cognitive impairment or AD (Fenech, 2017). To date, no RCT has been carried out for vitamin K and cognitive health outcomes (Fenech, 2017).

FATTY ACIDS

Fatty acids are components of the more complex lipids (e.g. triglycerides), which are important energy nutrients (Gropper, et al., 2009). Fatty acids can be categorized into SAFA (e.g. present in butter or margarine), mono unsaturated fatty acids (MUFA) (e.g. present in olive oil) and PUFAs (e.g. present in fatty fish) (Gropper, et al., 2009). PUFAs

can be divided into n-3 PUFAs and omega-6 (n-6) PUFAs, according to the place of the first double bond in the hydrocarbon chain (Hooijmans and Kiliaan, 2008). In general, fatty acids can be synthesized in the human body, however, two unsaturated fatty acids must be obtained from the diet, which are called essential fatty acids because enzymes delta 12 and 15 desaturases can be acquired from plant based foods only (Gropper, et al., 2009). These essential fatty acids are linoleic acid (LA) and alpha-linolenic acid (ALA) (Gropper, et al., 2009). Through LA, γ-linolenic acid (GLA), dihomo-γ-linolenic acid (DGLA) and arachidonic acid (AA) are formed (Gropper, et al., 2009). In addition, through ALA, EPA and DHA are synthesized (Gropper, et al., 2009). LA, GLA, DLGA and AA are known as n-6 PUFAs, and ALA, EPA and DHA as n-3 PUFAs (Gropper, et al., 2009). In the brain, fatty acids are abundantly present in the neuronal membrane (approximately 50 % PUFAs) and the myelin sheath (approximately 70 % PUFAs) (Hooijmans and Kiliaan, 2008). Aging, AD or all-cause dementia decreases the concentrations of n-3 PUFAs in the brain due to: (1) impaired transport of n-3 PUFAs, which decreases the abilitity of the fatty acids to cross the blood brain barrier, (2) oxidative stress causing lipid peroxidation, and (3) change in dietary intake of DHA and EPA (Hooijmans and Kiliaan, 2008). Due to these changes, the neuronal membrane fluidity decreases as n-3 PUFAs and cholesterol remain in the neuronal membranes, which in turn leads to an increase of eicosanoids which contribute to neuronal damages (Hooijmans and Kiliaan, 2008). The mechanisms described above make PUFAs promising fatty acids. The current state of knowledge will be outlined in the following section.

Omega-3 PUFAs - ALA is present in vegetable oils, such as linseed oil and soybean oil, leafy vegetables and nuts (Gropper, et al., 2009; van de Rest et al., 2012). Primary dietary sources of DHA and EPA are fatty fish or fish oils, for example salmon and tuna (Gropper, et al., 2009; van de Rest, et al., 2012). As mentioned earlier, DHA and EPA can be synthesized through ALA, however, only five to ten percent of ALA is used to form EPA and only one to five percent of ALA or EPA is used to form DHA (van de Rest, et al., 2012). Therefore, dietary intake of fatty fish or fish oil supplementation is important to include in the diet (van de Rest, et al., 2012). In the brain, DHA is the primary fatty acid, its concentration depends on dietary intake and changes across the life course (Hooijmans and Kiliaan, 2008). Together with EPA, DHA is abundandly present in the

neuronal membranes, where both enhance fluidity of the membranes by replacing n-6 PUFAs and cholesterol (Hooijmans and Kiliaan, 2008). This mechanism contributes to the amelioration of neurotransmission and signaling, consequently increasing the number of receptor bindings, neuroplasticity, and synapsis (Hooijmans and Kiliaan, 2008). Furthermore, DHA and EPA are involved in the clearence of the accumulation of Aß through IDE (Grimm et al., 2017). Both PUFAs enhance the non-amyloidogenic processing of APP leading to an increased α-secretase-cleaved soluble APP (sAPPα) secretion, which has a neurotrophic and neuroprotective function (Yanai, 2017). Also, both PUFAs have anti-inflammatory properties, which are used to deminish inflammation in the brain, resulting in an enhancement of Aß degradation (Grimm, et al., 2017). Previous prospective observational studies investigated ALA, EPA and DHA (Ammann et al., 2017; Cherubini et al., 2007; Conquer et al., 2000; Kroger et al., 2009; Laurin et al., 2003; Lopez et al., 2011; Samieri et al., 2008; Schaefer et al., 2006; van der Lee et al., 2018; Yamagishi et al., 2017). A meta-analysis (n= 25,872) demonstrated an association between high proportions of DHA and lower risks of all-cause dementia or AD (van der Lee, et al., 2018), but observational single studies have been inconclusive. Two studies (n =266 and 899) also reported an association between DHA and (incident) all-cause dementia or AD (Lopez, et al., 2011; Schaefer, et al., 2006). Additionaly, a longitudinal study (n= 6,706) demonstrated a relation between DHA plus EPA with all-cause dementia (Ammann, et al., 2017). However, one longitudinal study (n =1,214) reported an association between EPA and all-cause dementia, but did not report a relation for DHA or ALA (Samieri, et al., 2008). In addition, two studies (n= 945 and 935) observed a relation between ALA with incident all-cause dementia or with lower concentrations of ALA in dementia patients, but no significant associations were reported for DHA or EPA (Cherubini, et al., 2007; Yamagishi, et al., 2017). Moreover, one longitudinal study (n= 663) observed no associations at all (Kroger, et al., 2009). Furthermore, a systematic review including 3 RCTs (n= 632) performed in AD cases reported no effect of n-3 PUFAs supplementations in the treatment of AD (Burckhardt et al., 2016). In line with the systematic review, a recent RCT also observed no effect of a multinutrient supplement rich in n-3 PUFAs on cognitive function in elderly without cognitive impairment or with MCI (Baleztena et al., 2018). Lastly, a recent multidomain intervention including an intervention group receiving n-3 PUFAs, demonstrated no

effect of n-3 PUFAs supplementation alone on better free and cued selective reminding test performance, however, a multidomain intervention plus n-3 PUFAs supplemention had an effect on a better Trial Making Test (TMT) A performance (Chhetri et al., 2018).

Omega-6 PUFAs - LA can primarily be acquired from corn (oil), soybean (oil), sunflower seed (oil) or peanut oil, GLA from vegetable oils, and AA from lard, bacon, ham or walnuts (Gropper, et al., 2009; Russo, 2009). When n-6 PUFAs and n-3 PUFAs are consumed and formed according to the optimal ratio (n-6:n-3 ratio; <5:1), both groups tend to compensate each other's functions to enhance pathological conditions (Russo, 2009; Solfrizzi, et al., 2011). However, most of the time this is not the case and n-6 PUFAs have opposing effects to n-3 PUFAs due to their contribution to the formation of 'eicosanoids': prostaglandins, thromboxanes, leukotrienes, hydrox fatty acids and lipoxins (Simopoulos, 1999). In addition, n-6 PUFAs products contribute to thrombogenesis, atherogenic effects, and cell proliferation (Schmitz and Ecker, 2008; Simopoulos, 1999). Moreover, they also cause inflammation (Schmitz and Ecker, 2008; Simopoulos, 1999), which is in turn a pathway to dementia (Simopoulos, 1999). A limited number of studies reported on the association between n-6 PUFAs and dementia, which showed contradictive results (Heude et al., 2003; Kalmijn et al., 1997; Milte et al., 2011; Morris et al., 2003; Samieri, et al., 2008). Two longitudinal studies (n= 246 and 815) reported an association between high n-6 PUFAs intake (including LA and AA) and a reduced risk of AD (Morris, et al., 2003), or a higher odds for cognitive decline (Heude, et al., 2003). One cross-sectional study (n= 79) reported higher proportions of DGLA and AA in MCI participants in comparison to controls (Milte, et al., 2011). By contrast, two longitudinal studies (n= 1,214 and 5,386) reported no association between high proportions of LA or AA and incident AD or all-cause dementia (Kalmijn, et al., 1997; Samieri, et al., 2008).

OTHER NUTRITIONAL COMPOUNDS

In addition to vitamins and fatty acids other nutritional compounds may also be of interest in regards to cognitive health outcomes. Examples of other compounds which have been investigated previously with regard to cognitive health are given below. Oxidized-LDL (ox-LDL) will be studied further in this thesis and will therefore be elaborated on.

Oxidized-LDL - Ox-LDL is the result of the complex oxidation of LDL (Steinberg, 1997). It has been postulated that ox-LDL is produced by oxidized phospholipids which have been released from brain tissue into circulation (Chang et al., 2014). Furthermore, different parts of LDL can be oxidatively attacked such as the protein, the lipid moieties, sterols, fatty acids in phospholipids, cholesterol esters or triglycerides (Steinberg, 1997). Thus ox-LDL is the overall name for the group of ox-LDLs which contribute to the release of chemokines and cytokines (i.e. inflammatory pathway) from endothelial cells (Steinberg, 1997). Ox-LDL is known for its role in coronary heart diseases (CHD) and CVD (Holvoet et al., 2003; Toshima et al., 2000; Tsimikas et al., 2003), which in turn are risk factors for dementia. It has been hypothesized that ox-LDL might be a marker of oxidative damage in the human body and it might function as a secondary marker for the severity of oxidative damage in the presence of dementia (Chang, et al., 2014). To date, few studies have reported mixed results for ox-LDL and dementia. Two previous case-control studies reported higher concentrations of ox-LDL in AD participants as compared to controls (Aldred et al., 2010; Cai et al., 2007). However, two longitudinal studies (n= 572 and 670) reported no association between ox-LDL and MCI, risk of all-cause dementia, AD or vascular dementia (Koyama et al., 2013; Murr et al., 2014). To the best of our knowledge, no research groups have investigated the association between ox-LDL and cognitive function.

Homocysteine - Homocysteine is a non-essential amino acid which is synthesized in the methionine cycle to convert the essential amino acid methionine into the semi-essential amino acid cysteine (Kennedy, 2016). In particular, low concentrations of folate, vitamin B6, and/or vitamin B12 leads to an increased concentration of homocysteine, which in turn leads to damaging effects including an increased rate of oxidative stress, aggregation of Aβ and hyper-phosphorylation of tau, and affects the vascular circulation in the brain (Kennedy, 2016).

Minerals - Zinc has been reported to be essential for learning and memory (Kawahara et al., 2018) and magnesium contributes to neuronal signaling (Dominguez and Barbagallo, 2018). On the other hand, accumulation of iron and copper results in brain damage (Kalli, 2017), which selenium fights against (Aaseth et al., 2016).

Polyphenols - Polyphenols can be categorized into flavonoids (25-50 %) (e.g. anthocyanins and flavan-3-ols) and nonflavonoids (e.g. resveratrol and gallic acid) (Solfrizzi, et al., 2011). These compounds contain antioxidant properties which are used to counteract oxidative stress, to scavenge Aß aggregation and to protect the brain against neurotoxicity (Hu, et al., 2013).

1.7.2. FOOD GROUPS AND INDIVIDUAL FOODS

In the past decades, studies have investigated individual foods in relation to DM and CVD (Bechthold et al., 2017; Schwingshackl et al., 2017). Both diseases are risk factors for dementia, therefore these foods have also received increased interest for cognitive health. In this section the current state of knowledge will be outlined for particular individual foods or food groups that have been previously investigated with respect to DM and CVD.

Fruits and vegetables - Fruits and vegetables are two important food groups which play a pivotal role in the prevention of CVD, consequently both groups might have a role in the prevention or delay of dementia (Barberger-Gateau et al., 2007). The underlying mechanism of the beneficial effects of fruits and vegetables on cognitive function or dementia is primarily counteracting oxidative stress and inflammation (Barberger-Gateau, et al., 2007). Both food groups are rich in compounds with anti-oxidative and/or anti-inflammatory properties (e.g. vitamin C and vitamin E) (Morris et al., 2006; Nooyens, 2015). Several observational studies have been carried out to examine the relation of fruits and vegetables and cognitive decline or all-cause dementia. A recent systematic review and meta-analysis (2017) including 31,104 individuals from 9 studies, of which 5 were longitudinal studies, revealed that increased fruits and vegetables intake was associated with a reduced risk of cognitive impairment and dementia, although a secondary analysis revealed that the association was driven by fruits (Jiang et al., 2017). A second systematic review and meta-analysis (2017) was in line with these findings (Wu et al., 2017b).

Whole grains - Whole grains have been investigated in relation to CVD and DM (Bechthold, et al., 2017; Schwingshackl, et al., 2017). These are foods rich in fiber such as oatmeal, brown rice or barley, or ingredients of foods such as in bread and in cereals (Mobley et al., 2013). The beneficial effects of whole grains can primarily be attributed to

fiber and phytonutrients (Bechthold, et al., 2017; Jonnalagadda et al., 2011). These nutrients have antioxidant and anti-inflammatory compounds which are used to fight against oxidative stress and inflammation (Bechthold, et al., 2017; Jonnalagadda, et al., 2011). Two recent studies, one longitudinal (n= 2,223) and one cross-sectional (n= 894) investigated the association between higher whole grains intake and cognitive function or cognitive decline, but both studies failed to observe an association (Dong et al., 2016; Shakersain et al., 2018). To the best of our knowledge, no studies have investigated dementia or conducted an RCT yet.

Dairy products - Dairy products such as milk, yoghurt or cheese are abundant in vitamin D, phosphorus, and magnesium (Crichton et al., 2010). These compounds, which have antioxidant and anti-inflammatory properties, play important roles as they protect and regulate the vascular system, improve insulin sensitivity, or prevent brain structure damages that occur with cognitive decline (Crichton, et al., 2010). Wu et al. (2016) conducted a systematic review and meta-analysis including 10,941 individuals from 7 studies (including 4 longitudinal studies). The authors reported that higher milk intake, as compared to low intake, was associated with a decreased risk of cognitive decline, all-cause dementia or AD (Wu and Sun, 2016). However, a recent large (n= 13,751) longitudinal study observed that milk intake at least once per day, was associated with a faster decline of cognition (Petruski-Ivleva et al., 2017).

Fish - It has been postulated that PUFAs intake, such as salmon or tuna, is associated with reduced risk of cognitive decline and all-cause dementia (Hu, et al., 2013). The association is thought to be primarily driven by n-3 PUFAs (i.e. EPA and DHA), which have been explained in greater detail earlier**.** Previous observational studies point towards a beneficial association between fish intake and cognitive function, cognitive decline or dementia (Samieri et al., 2018; van de Rest et al., 2016; Zhang et al., 2016). A systematic review and meta-analysis (2016) including 181,580 individuals from 21 longitudinal studies reported that higher fish intake was associated with a lower risk of AD or all-cause dementia (Zhang, et al., 2016). In addition a pooled analysis including 23,688 individuals from five studies revealed that higher fish intake was associated with slower cognitive decline (Samieri, et al., 2018).

Eggs - Eggs are well known to contain proteins and lipids, in particular cholesterol (Solfrizzi et al., 2017). On the other hand, eggs have a high content of vitamins and carotenoids (e.g. A, B6, B12, riboflavin, folic acid, lutein and choline), and minerals (e.g. iron, calcium, phosphorus and potassium) (Solfrizzi, et al., 2017). These compounds. counteract oxidative stress, inflammation and contribute to protect the brain for structural changes. To date, two cross-sectional studies reported on cognitive health outcomes. One study (n= 404) demonstrated that higher eggs intake was associated with lower odds of MCI (Zhao et al., 2015). By contrast, the second study (n= 894) observed no association between higher eggs intake and cognitive function (Dong, et al., 2016).

Olive oil - Olive oil is a major component of the Mediterranean diet. It contains a high percentage of MUFAs (70-80 %: oleic acid), the presence of PUFAs (7-8 %: LA and ALA), and polyphenolic compounds (Solfrizzi, et al., 2011). The underlying mechanisms of its potential protective effect on cognitive decline might be driven by its anti-oxidative and anti-inflammatory compounds that scavenge oxidative stress and inflammation, which in turn are causal pathways for dementias (Hu, et al., 2013; Solfrizzi, et al., 2011). Two longitudinal studies (n= 2,223 and 6,947) reported an association between higher olive oil intake and slower verbal fluency decline, visual memory decline or cognitive decline (Berr et al., 2009; Shakersain, et al., 2018). The Prevención con Dieta Mediterránea (PREDIMED) trial assessed the Mediterranean diet plus olive oil, and the Mediterranean diet plus mixed nuts, as compared to controls, in relation to cognitive function (Valls-Pedret et al., 2015). Participants who were assigned to the Mediterranean plus olive oil group had a greater performance on executive measure of attention, as compared to the other groups (Valls-Pedret, et al., 2015).

Nuts - Nuts are a rich source of multiple micronutrients such as PUFAs (n-3 and n-6) MUFAs, minerals, vitamins, protein and fiber (Bechthold, et al., 2017; Solfrizzi, et al., 2017). As described above, the majority of these compounds are beneficial for brain health, as they counteract oxidative stress and inflammation. Although nuts are a rich source of the aforementioned components, few studies have investigated nut intake and have reported mixed results (Nooyens et al., 2011; O'Brien et al., 2014; Samieri et al., 2013a; Samieri et al., 2013c). For example, a large longitudinal study including 16,058 individuals demonstrated that higher nut intake was associated with better average

cognitive function (Samieri, et al., 2013c). In contrast, a large longitudinal study including 6,174 participants reported no association between higher nut intake and global cognition or verbal memory (Samieri, et al., 2013a).

Red meat and processed meat - Red meat and processed meat are well known risk factors for CVD, stroke, DM and colorectal cancer (Yip et al., 2018). Several biological mechanisms have been suggested, for example, red meat and processed meat are rich in SAFA which may change peripheral and brain lipid homeostasis, which in turn may damage neuronal membrane properties, change synaptic plasticity, affect the communication between neurons and contribute to the accumulation of Aβ (Granic et al., 2016). Otherwise, meat contains high-quality protein (Jakobsen et al., 2011) and other essential compounds such as vitamin B12 and functional components with possible benefits for cognitive functioning (Azhar et al., 2013). Red meat and processed meat have not been widely studied with regard to cognitive health outcomes. One large observational study including 14,960 individuals reported that higher red meat intake was associated with an increased odds ratio of all-cause dementia (Albanese et al., 2009).

Alcohol - Moderate alcohol intake might be protective against cognitive decline or dementia, either through alcohol intake itself and/or through the antioxidant effects of beneficial compounds, for example, represented in red wine (Solfrizzi, et al., 2011). Alcohol intake has been widely studied in cognitive health outcomes. An umbrella review (2015) including 45 studies from three systematic reviews demonstrated that light to moderate alcohol consumption was associated with a decreased risk of AD and all-cause dementia (Ilomaki et al., 2015). Furthermore, a large prospective study including 5,033 individuals investigated the association between the intake of different alcoholic beverages and cognitive function after seven years and demonstrated that moderate wine intake was associated with better cognitive function test performance (Arntzen et al., 2010). On the other hand, alcohol use disorders due to high alcohol intake have been associated with an increased risk for all-cause dementia in a large nationwide retrospective cohort including 19,769,440 individuals (Schwarzinger et al., 2018).

Coffee - Over the years coffee consumption has received great interest in relation to cognitive decline or dementia (Liu et al., 2016; Panza et al., 2015; Wu et al., 2017a).

Coffee is a source of many possible protective compounds that might act against pathways leading to dementia (Panza, et al., 2015). A major compound in coffee is caffeine which has a neuroprotective effect attributed to its competitive antagonism of excessive activation of adenosine (i.e. contributes to energy transportation) receptors in the brain (hippocampus and cortex, in particular) (Panza, et al., 2015). Caffeine is thought to suppress ß-secretase and y-secretase, consequently contributing to the reduction of neuronal damage caused by Aß accumulation (Arendash et al., 2009; Arendash et al., 2006; Panza, et al., 2015). Furthermore, caffeine has a role in the inflammatory pathway by acting against pro-inflammatory cytokines such as TNF-α, IL-12 (Cao et al., 2009), Other important compounds in coffee are magnesium (de Valk, 1999) potassium, vitamin B3, tocopherols, and polyphenols (Panza, et al., 2015). A systematic review and meta-analysis (2017) including 34,282 individuals from nine longitudinal studies examined the relation between higher coffee intake with the risk of cognitive disorders (i.e. AD, all-cause dementia, cognitive decline, and cognitive impairment) (Wu, et al., 2017a). The authors reported that the consumption of one or two cups of coffee per day, as compared to less than one cup, was associated with a decreased risk of the development of cognitive disorders (Wu, et al., 2017a). Although, a second systematic review observed a relation with a decreased risk of AD, but not with cognitive decline (Liu, et al., 2016).

Green tea - Green tea -rich in antioxidants- might be a promising contributor to the prevention or delay of cognitive decline or dementia. Green tea contains polyphenols, of which Epigallocatechin-3-galate (EGCG) has received interest as it contributes to the attenuation of Aß formation, *APP* expression in the hippocampus, and scavenges ROS in the oxidative stress pathway (Hu, et al., 2013; Venkatesan et al., 2015). Furthermore, tea contains L-theanine (i.e. free amino acid) and caffeine, which both contain neuroprotective properties (Song et al., 2012). At present, a limited number of longitudinal observational studies have studied the relationship between green tea and cognitive decline or dementia (Arab et al., 2013; Feng et al., 2010; Liu et al., 2017; Noguchi-Shinohara et al., 2014; Panza, et al., 2015). However, most studies point towards a beneficial effect of green tea on cognitive health. A meta-analysis and a dose-response meta-analysis including 48,435 individuals from 17 observational studies reported that higher green tea intake was associated with a lower odds of cognitive

impairment and cognitive decline, but not with incident all-cause dementia (Liu, et al., 2017).

Sugar sweetened beverages (SSB) – There is a large body of evidence linking SSB with type two diabetes mellitus (T2D) and CVD (Malik and Hu, 2015). Particularly fructose which is present in SSB, contributes to lipogenesis in the liver, which in turn may lead to weight gain and obesity when SSB are consumed on a regular basis (Malik and Hu, 2015). Also, fructose contributes to insulin resistance, which in turn is a risk factor for T2D (Malik and Hu, 2015). Currently, SSB intake has not been evaluated in a systematic review in relation to cognitive health outcomes. Evidence is limited and inconclusive. A cross-sectional study (n= 737) reported that higher SSB intake, as compared to low intake, was associated with a higher odds for cognitive impairment (MMSE <24) (Ye et al., 2011). By contrast, a large longitudinal study (n= 1,484) investigated the association between higher SSB intake and all-cause dementia or AD and reported that higher SSB intake, as compared to no intake, was not associated with incident all-cause dementia or AD (Pase et al., 2017).

1.7.3. DIETARY PATTERNS

Examining individual nutrients or foods can be challenging as nutrients or individual foods are not consumed in isolation, therefore the association under study might be driven by interactions between nutrients or individual foods (Hu, 2002; Jacobs and Steffen, 2003). As combinations of foods are the units we eat during the day, investigating dietary patterns might be of interest (Bruun et al., 2007; Jacobs and Tapsell, 2007). Also, results yielded from dietary pattern analyses are informative for public health purposes such as the development and evaluation of dietary guidelines. Dietary patterns can be analyzed in different ways; according to existing dietary guidelines (*a priori*) and using a data driven approach (*a posteriori*).

A PRIORI DIETARY PATTERNS

Over the years a variety of *a priori* dietary patterns have been developed, based on beneficial traditional eating habits (e.g. the Mediterranean diet), recommendations from international (e.g. World Health Organization; WHO) and national health authorities (e.g. the Healthy Eating Index; HEI), or based on the prevention of chronic diseases (e.g. the

Dietary Approach to Stop Hypertension; DASH) (Schulze et al., 2018). Below an outline is given of the most prominent a priori patterns studied.

The Mediterranean diet - This diet has been widely studied in relation to major chronic diseases and it is the richest diet in antioxidants (Dinu et al., 2018). The Mediterranean diet is characterized by a high intake of fruits, vegetables, olive oil, nuts, legumes, beans, fish and non-refined grains, and a moderate intake of dairy, meat and alcohol (Trichopoulou et al., 2003). A recent umbrella review (2018) including 12,800,000 individuals from 13 meta-analyses of observational studies and 16 meta-analyses of RCTs reported on the relation between adherence to the Mediterranean diet with 37 health outcomes (Dinu, et al., 2018). The authors demonstrated that higher adherence to the Mediterranean diet was associated with a decreased risk of CVD and DM, which in turn are risk factors for dementia (Dinu, et al., 2018). Furthermore, the authors demonstrated that a higher adherence to the Mediterranean diet was associated with a decreased risk of MCI, AD or all-cause dementia (Cao et al., 2016; Psaltopoulou et al., 2013; Singh et al., 2014; Wu and Sun, 2017). Furthermore, the PREDIMED trial investigated a Mediterranean type diet rich in olive oil or rich in nuts and cognitive performance (Martinez-Lapiscina et al., 2013). The authors reported that participants who adhered to the Mediterranean type diet had a higher cognitive performance as compared to the control group (Martinez-Lapiscina, et al., 2013). By contrast, the Mediterranean diet for cognitive function and cardiovascular health in the elderly (MedLey) trial which examined a Mediterranean type diet in relation to cognitive function reported no better performance on the cognitive tests by individuals adhering to the Mediterranean type diet as compared to controls (Knight et al., 2016).

Dietary Approach to Stop Hypertension - The DASH diet has been developed to test the effects of diet on blood pressure, consequently to prevent or treat hypertension (Appel et al., 1997; Sacks et al., 1995). The diet is characterized by a high intake of fruit, vegetables, wholegrains and nuts, moderate intake of fish, poultry and low-fat dairy products, and a low intake of meat, sugar and processed foods (Appel, et al., 1997). The latest systematic review and meta-analysis (2015) including 1,917 individuals from 20 RCTs reported a relationship between adherence to the DASH diet and cardiovascular

risk factors (Siervo et al., 2015). In addition, adherence to the DASH diet has also been shown to reduce the risk of diabetes (Knowler et al., 2002). Studies investigating the DASH diet and cognitive health outcomes are few, however, one large (n= 960) longitudinal study reported that the diet was associated with a slower rate of cognitive decline and a decreased incidence of AD (Morris et al., 2015a; Morris et al., 2015b; van de Rest et al., 2015). Evidence from intervention studies is limited, however, one RCT has reported that participants with high blood pressure who adhered to the DASH diet had a better psychomotor speed as compared to controls (Smith et al., 2010; van de Rest, et al., 2015).

Mediterranean - DASH Intervention for Neurodegenerative Delay diet (MIND) - Until 2015 no *a priori* dietary pattern existed which included specific foods or food groups that protect the brain against neurodegeneration (Morris, 2016). Therefore, a research group from Rush University in Chicago developed the MIND diet, which is a combined dietary pattern of the Mediterranean and the DASH diet with some modification (Morris, 2016; Morris, et al., 2015a). The basic components of the three diets are the same (Morris, 2016), but based on previous literature berries and green leafy vegetables were added as additional groups into the MIND diet (Morris, 2016). The authors reported that higher adherence to the MIND diet was associated with slower cognitive decline (n= 923) and decreased incident AD (n= 960) (Morris, et al., 2015a; Morris, et al., 2015b). Consecutive studies (range: n= 2,223-16,058) have reported mixed results. Associations were found for cognitive performance (McEvoy et al., 2017), and slower cognitive decline (Shakersain, et al., 2018), but one study did not report an association with cognitive decline (Berendsen et al., 2018).

Diet Inflammatory Index (DII) - The DII is based on literature research created to categorize dietary patterns according to their level of inflammation; from maximally anti-inflammatory to maximally pro-inflammatory (Cavicchia et al., 2009; Shivappa et al., 2014). The DII consists of 45 food parameters including micronutrients (e.g. vitamins), macronutrients (i.e. carbohydrates), single foods (e.g. onion) and total energy intake (Shivappa, et al., 2014). A new meta-analysis (2018) including two case-control studies, 11 longitudinal studies and one cross-sectional study, demonstrated that individuals, in

particular in the highest category (i.e. pro-inflammatory), had an increased risk of CVD (Shivappa et al., 2018). No systematic review exists for cognitive health. A longitudinal study (n= 7,085) reported that individuals with a higher DII score had an increased risk of MCI and dementia (Hayden et al., 2017) and a second study (n= 1,723) showed that individuals with the highest DII score had a lower performance on both memory and cognitive test performance (Frith et al., 2018).

Healthy Diet Indicator (HDI) - In 1990 the World Health Organization (WHO) published a dietary guideline to prevent chronic diseases (World Health Organisation, 1990). In 1997 Huijbregts et al. developed the HDI to examine the WHO guideline in relation to chronic diseases (Huijbregts et al., 1997). In 2014 Jankovic et al. updated the HDI according to the WHO guideline of 2004 (Jankovic et al., 2014; Nishida et al., 2004). The new HDI included moderate components (SAFA, mono- and disaccharides, cholesterol), moderation range components (PUFAs and protein) and adequacy components (fiber and fruits and vegetables) (Jankovic, et al., 2014). To date, one study including 21,837 participants from three cohorts investigated the association between adherence to the new HDI and cognitive decline and reported no association between a higher adherence to the HDI and a decreased rate of cognitive decline (Berendsen et al., 2017).

Healthy Eating Index - Several versions of the HEI exist including the original, HEI-2005, HEI-2010 and the alternate HEI or the alternate HEI-2010 (Chiuve et al., 2012; Guenther et al., 2013; Guenther et al., 2008; Kennedy et al., 1995; McCullough et al., 2002). The HEI-2010 includes fruits, vegetables, green vegetables/peas and beans, whole grains, dairy, protein food, MUFAs and PUFAs. In addition, the index includes non-preferred food components, namely, refined grains, sodium, empty calories, high fat dairy, SAFAs, and trans fatty acids (Guenther, et al., 2013). A recent systematic review and meta-analysis (2018) including 1,670,179 individuals from 34 cohort studies examined the HEI scores and the alternate HEI scores (Schwingshackl et al., 2018). Meta-analyses revealed that adherences to the HEI scores were associated with a reduced risk of cardiovascular disease mortality or incidence and T2D, but not with neurodegenerative diseases (i.e. MCI, probable dementia or cognitive decline) (Schwingshackl, et al., 2018). However, adherences to the alternate HEI scores were

associated with a decreased risk of MCI, probable dementia or cognitive decline (Schwingshackl, et al., 2018).

Nordic diet - The Nordic diet is the 'Mediterranean diet' of the north. Due to differences in food consumption and availability of foods in Nordic countries, it is rather difficult for individuals living in Finland or Norway to adhere to the Mediterranean diet (Kanerva et al., 2013). In 2013 the diet was transformed into a diet score for assessment in cohort studies (Kanerva, et al., 2013). The diet advices a high intake of fruits and berries, vegetables, cereals, low-fat milk, fish and a low intake of meat products (Kanerva, et al., 2013). Currently, two large studies (n= 1,140 and 2,223) have reported associations between the Nordic diet and memory or cognitive decline (Mannikko et al., 2015; Shakersain, et al., 2018).

Other diets – Examples of other diets that have been linked to chronic diseases such as diabetes and CVD are: vegetarian (Dinu et al., 2017; Lee and Park, 2017), vegan (Dinu, et al., 2017) Paleolithic (Whalen et al., 2017), and gluten-free (Lebwohl et al., 2017) diets (Schulze, et al., 2018).

A POSTERIORI DIETARY PATTERNS

Dietary guidelines to promote healthy eating are established for the general population, therefore it is of interest to investigate the general population to provide insight into their general eating habits. However, dietary habits are evolving, to account for this it is important to explore new dietary patterns. On the other hand one should be cautious as the extracted patterns cannot always be distinguished into a 'healthy' pattern and an 'unhealthy' pattern (Hodge and Bassett, 2016), and associations cannot always be replicated by other studies (Schulze, et al., 2018). Several methods exist to extract dietary patterns from the data using a statistical approach, examples are; cluster analysis, principal component analysis (PCA), reduced rank regression (RRR), and treelet transform (TT) (Hodge and Bassett, 2016; Schulze, et al., 2018).

1.6. DIETARY ASSESSMENT METHODS

Diet can be assessed with the use of several assessment tools, the most frequent tools being the 24 hour dietary recall method, food record method, the food frequency method, and the dietary history method. In addition, dietary biomarkers are used to measure nutrient status. An outline of these methods are given in this paragraph.

24hour dietary recall method - The 24hour dietary recall method is an indepth 20-30 minutes face-to-face or phone interview between a trained dietary interviewer and a study participant (Hu, 2008; Willett, 1998). Participants are asked about their dietary intake of the previous day or 24 hours (Hu, 2008). This assessment method relies completely on the participants' short-term memory (Willett, 1998). A variation of the classic 24hour dietary recall method is the multiple-pass 24-hour recall method, in which the interview is split up in five consecutive steps (Hu, 2008; Willett, 1998). In order for the interview to be objective, the interviewer is trained to ask open-ended questions in a nonjudgmental manner, however, under reporting may still occur (Hu, 2008; Willett, 1998). For large cohort studies it is often not feasible to use this method, however, one can choose to implement this method in a subset of the cohort (Hu, 2008).

Food record method - A food record or food diary is a list of consumed foods and drinks from a participant on one or multiple days (Buzzard et al., 1996). It is important for participants to be trained beforehand to enhance the accuracy and completeness of the record (Willett, 1998). The quantification of the record can either be done by weighing or by determining household volumes (Hu, 2008). In contrast to the 24hour dietary recall method, a major advantage of this method is that it does not rely on short-term memory as participants are asked to report their food or drink intake at the time of consumption (Willett, 1998). However, the method does require highly motivated participants and is a challenge for large cohort studies (Hu, 2008).

Food frequency Questionnaire (FFQ) – The FFQ is predefined and developed to assess usual intake over a long period of time (Willett, 1998). The questionnaire consists of a food list and a frequency section (Willett, 1998). However, it is a challenge to develop a FFQ which covers the whole diet of the population under study, particularly if it is a multiethnic population (Willett, 1998). Furthermore, to account for total energy

intake in nutrition epidemiological analyses it is important that most frequent consumed foods are included in the FFQ (Willett, 1998). attention must be given to the frequency section, as too few frequency options might led to a loss of information (Willett, 1998). The development of the FFQ can be done in several ways, for example one could consider to include portion sizes or serving sizes (e.g. a glass of milk) into the frequency question, also known as a semi-quantitative questionnaire (Willett, 1998). In nutrition epidemiology studies this method is often used as it is possible to rank participants according to their average intake over a long period of time, they are easy to implement and to process, and FFQs are not considered as a burden for the study participants (Willett, 1998). On the other hand, the FFQ lacks specificity, which makes it difficult to estimate absolute nutrient intake, food product changes require updates of the FFQ, and random and systematic errors may occur as the FFQ is based on self-report and relies on memory (Hu, 2008).

Dietary history method - The dietary history method is a combination of an interview, a cross-check FFQ and a 3-day food record which aims to assess usual food consumption patterns (Hu, 2008). The major advantage is the specificity on long term dietary intake information (Hu, 2008). However, limitations of this method are that the interview could take up to two hours, processing the data is time consuming, and it is expensive and difficult to standardize (Hu, 2008). For nutrition epidemiology studies it is not always feasible to implement this method because of time and costs (Hu, 2008).

Biomarkers for nutrient intake - The use of biomarkers for nutrient intake assessment are of great interest as they are sensitive to intake, reliable and objective (Hu, 2008). It is important for a biomarker to reflect the long-term cumulative effect of a dietary exposure in order to investigate the relation between the nutrient of interest with chronic diseases (Hu, 2008). To date, there is not a biomarker for every nutrient yet, however, some established biomarkers do exist (Hu, 2008). At first, the 24-hour urinary nitrogen (i.e. the collection of 24 hour urine samples) method is used as an unbiased biomarker for protein intake (Bingham and Cummings, 1985). The method is a burden for participants and not easy to implement in cohort studies (Hu, 2008). Second, the 24-hour urine sodium and potassium method is used to determine valid biomarkers of sodium and potassium (Kesteloot and Joossens, 1990). Due to the large day-to-day variation

multiple 24-hours urine samples are required, which is a burden on the participant (Hu, 2008). Third, plasma fasting triglycerides are used as an indirect marker for both total fat and carbohydrate intake (Baylin and Campos, 2006; Hu, 2008). Fourth, to estimate the intake of fatty acids plasma, erythrocytes, platelets, and adipose tissue fatty acids can be used (Baylin and Campos, 2006; Hu, 2008). However, fat present in adipose tissue is considered the gold standard, as the tissue has a slow turnover rate (Hu, 2008). Fifth, serum, plasma or red blood cells (RBC) folate can be used as a biomarker for folate intake, where serum or plasma folate reflect short-term intake and RBC reflect up to four months (Mason, 2003). Sixth, serum cobalamin is used as a biomarker for vitamin B12 and pyridoxial-5'-phosphate for vitamin B6 (Hu, 2008). Seventh, biochemicals in urine or blood can be used as biomarkers for isoflavones and lignans, however, these biochemicals reflect only short-term intake (Hu, 2008; Willett, 1998). Eighth, plasma ferritin or soluble transferrin receptor (sTfR) concentrations can be used as biomarkers for iron intake or iron deficiency (Hambidge, 2003; Hu, 2008). Ninth, selenium present in plasma, RBC and toenails can be used as biomarkers for selenium intake, where selenium in toenails is considered the gold standard due to its slow turnover rate (Swanson et al., 1990). Additionally, toenails can also be used to measure chromium, magnesium, zinc, and copper (Hu, 2008). Lastly, the doubly labeled water (DLW) method (i.e. oral administration of weighed dose of water containing stable isotopes deuterium and oxygen-18, which is collected from the urine or blood plasma over 15 days), is used to determine energy expenditure (Hu, 2008; Speakman, 1997). This method is expensive but highly accurate and precise (Hu, 2008).

In summary, the number of people with dementia is increasing (Blennow, et al., 2006; Jicha and Carr, 2010). Many detrimental and protective factors that affect the risk of dementia have been identified through research, including age, *APOE* ε4 status and a family history of the disease of which cannot be modified (Winblad, et al., 2016). Thus, dementia is a challenging on going global public health burden on society, which needs targeted research strategies to identify treatments to delay the onset of the disease, to slow disease progression or to cure dementia (Winblad, et al., 2016). Nutrition is an important modifiable lifestyle factor throughout the lifespan. A growing body of evidence points to an important role of nutrition in the development of dementia and its progression rate (Gustafson, et al., 2015), however, many gaps still exist. There is a

solid body of observational evidence for vitamin B6, folate, B12, and vitamin C, however, RCTs failed to demonstrate an effect. In addition, vitamin A, beta-carotene, vitamin K and ox-LDL may play a pivotal role in the brain, but epidemiological evidence is primarily based on small studies and the evidence is limited and inconclusive. In contrast, vitamin D has been widely studied in large observational studies, but evidence is contradictive and RCTs are inconclusive. Epidemiological evidence of fatty acids (i.e. SAFA, MUFA, PUFA) is primarily based on n-3 PUFAs. Strikingly, evidence from RCTs is inconclusive. In addition, other nutritional compounds that deserve further study are homocysteine, minerals and polyphenols. Furthermore, most studied individual food intake or food group intake are fruits and vegetables, fish, alcohol, and coffee. Additionally, most promising evidence has been reported for fruits and vegetables, fish, alcohol, and coffee intake. Also, limited evidence of red meat and processed meat on cognitive health hints towards a harmful effect. Interestingly, olive oil, the primary component of the Mediterranean diet, has not been widely studied with regard to cognitive health, but the PREDIMED RCT demonstrated promising results. Also, promising, although observational, evidence has been reported for green tea. In contrast, studies investigating whole grain, dairy products, eggs, nuts and SSB have reported conflicting results. Lastly, adherence to a priori dietary patterns (Mediterranean diet, DASH, MIND, and Nordic diet) has shown to be beneficial, whereas a higher DII score might be harmful. In contrast, evidence for the HDI and HEI is contradictive. Also, evidence from RCTs is abundant for the Mediterranean diet and the DASH diet, but is limited for the other diets. Hence, one should keep in mind that a posteriori patterns obtained from the data might give new insights into the evolving dietary patterns of the population under study.

1.8 OBJECTIVES

Currently, evidence from longitudinal observational studies on the associations between nutrition and AD, all-cause dementia, cognitive function or cognitive decline overall suggest that nutrition plays an important role in the disease process. However, longitudinal observational studies have reported contrasting findings. In addition, studies in a German population are very limited. Also, studies have been conducted in the elderly, but not that many in the oldest old. According to the above, there is a pressing need to replicate previous studies in a longitudinal study design and to investigate previous observational relations in the oldest old. Furthermore, investigating a whole diet can be challenging as it is not clear which specific nutrient, nutrient group, food or food group is the main contributor to the beneficial or harmful effect of the diet on the disease under study. Therefore, investigating nutrition on multiple levels in relation to dementia can give further insights in the prevention, delay or treatment of dementia.

The objective of this thesis was to investigate the role of nutrition in German elderly and oldest old on AD, all-cause dementia and memory decline, with the use of individual nutrients, individual foods and food groups, in a population-based longitudinal cohort study. The first aim was to examine the association between vitamins and ox-LDL and AD or all-cause dementia in German oldest old. The second aim was to investigate the association between n-3 and n-6 PUFAs, and AD or all-cause dementia in German oldest old. The third aim was to assess the relation between individual foods and food groups with memory decline and AD in German elderly.

2 GENERAL MATERIAL AND METHODS OF THE PRESENTED STUDIES

2.1. STUDY DESIGN

The studies presented in chapters 3.1., 3.2. and 3.3. of this thesis are from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe); and Needs, health service use, costs and health-related quality of life in a large sample of oldest-old primary care patients (AgeQualiDe). The study is a German multicenter and general practitioner (GP) registry-based prospective cohort study on early detection and prediction of mild cognitive impairment and dementia in elderly primary care patients starting in 2003. Enrolled participants were primary care patients aged 75 years or older living in urban areas of six German cities: Bonn, Düsseldorf, Hamburg, Leipzig, Mannheim or Munich. The recruitment and baseline visits were conducted between January 2003 and November 2004. Since then, eight follow-up (FU) visits (with an 18-month interval between each FU) were completed up to the time of the presented studies. Selection and sampling of the participants have been described previously (Jessen et al., 2011; Luck et al., 2007). Participants were recruited by 138 GPs connected to the respective study sites (Jessen, et al., 2011; Luck, et al., 2007). Of the GP population of 22,701 persons, a total of 10,850 were eligible for inclusion in the study. Of those, 6,619 persons were randomly selected to be invited to participate in the study. Inclusion criteria were age above 75 years, absence of dementia (Cooper et al., 1992), and at least one personal contact with the GP during the past year. Exclusion criteria were consultations only via home visits, residence in a nursing home, prevailing severe illness with an expected fatal outcome within the next three months, insufficient German language skills, blindness or deafness, inability to provide an informed consent, and not being a regular patient of the participating GP. Of the 6,619 invited persons, 3,327 persons consented to enrollment and were investigated at baseline. All (baseline) assessments were performed by trained investigators (physicians, psychologists, gerontologists) at the participants' homes and included structured clinical interviews comprising sociodemographic and anthropometric information, neuropsychological tests, current physical and mental health, and psychosocial and lifestyle factors. The same personal structured interviews and neuropsychological assessments were conducted in subsequent FUs at 18-month intervals. For participants who could not be interviewed

personally at any FU visit, informant-based information was obtained. In such a case, participants were excluded from further FUs. The study was approved by the local ethics committees of the six participating centers, and all participants gave their written informed consent to the study.

2.2. ASSESSMENT AND DIAGNOSIS OF DEMENTIA

Dementia was diagnosed by consensus of the interviewing investigator and an experienced geriatrician or geriatric psychiatrist according to DSM-IV and International Statistical Classification (ICD-10) criteria that are implemented as a diagnostic algorithm in the structured interview for the diagnosis of a dementia (SIDAM) (Zaudig and Hiller, 1996; Zaudig et al., 1991). This algorithm comprises cognitive impairment, as defined by the total SIDAM cognitive score (SISCO, scoring 0-55 with a higher score indicating a better performance as the sum of the MMSE score (0-30) and 25 additional items) and impairment of activities of daily living (ADL) as defined by a score of at least two points on the SIDAM-ADL-scale. For dementia, the etiological diagnosis of AD was established according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (McKhann et al., 1984). For the diagnosis of vascular dementia, that is, in case of evidence for cerebrovascular events (Hachinski-Rosen Scale, medical history) and a temporal relationship between the cerebrovascular event and the occurrence of cognitive decline, the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l´Enseignement en Neurosciences (NINDS-AIREN) criteria were used (Roman et al., 1993). Mixed dementia was diagnosed in cases of cerebrovascular events without temporal relationship to cognitive decline. Dementia diagnosis in participants who were not personally interviewed was based on the Global Deterioration Scale (GDS) (Reisberg et al., 1982) and the Blessed Dementia Rating scale (BDR) (Blessed, 1996). A score of 4 or higher on the GDS was used as the criterion for the dementia diagnosis. In these cases, an etiological diagnosis was established if the information provided was sufficient to judge etiology according to the criteria named above. For statistical analyses AD and mixed dementia were combined into one AD group.

2.3. NEUROPSYCHOLOGICAL ASSESSMENT

In addition to the cognitive scale in the SIDAM, participants were assessed with subtests of the CERAD neuropsychological assessment battery, which was designed to cover the cognitive domains most commonly affected in AD dementia (Morris, et al., 1989). The administered CERAD subtests varied across FUs, but always included the immediate and delayed verbal memory subtests of the CERAD. In the present study, we used the 10-item Word List Immediate Recall subtest (score 0-30), the 10-item Word List Delayed Recall subtest (score 0-10), and the 10-item Word List Recognition subtest (scored by subtracting False Alarms from Hits; score 0-10) to quantify objective episodic memory performance. Higher scores indicate a better memory performance in all subtests. From these subtests we created one overall memory score by standardizing a single subtest to percentages of its possible maximum score (i.e. dividing the respective score by its maximum score and multiplying the result by 100) and averaging the resulting three standardized subtest scores to a total CERAD memory score (range 0-100).

2.4. BLOOD CONCENTRATIONS OF VITAMINS A, D, E, BETA-CAROTENE AND OX-LDL

Blood was collected by participants' GPs in tubes with Ethylenediaminetetraacetic acid (EDTA) without anticoagulant, and stored at -80 °C. For determination of vitamins A and E and beta-carotene, the plasma samples were deproteinized by the addition of ethanol (containing apocarotenal as the internal standard, five micromol per litre (µmol/l)). Fat-soluble vitamins were extracted with n-hexane and analysed using normal-phase high-performance liquid chromatography (HPLC) and ultraviolet detection. Plasma ox-LDL (Immundiagnostik, Bensheim, Germany) and serum vitamin D (25-hydroxy-cholecalciferol) (IDS, Frankfurt/Main, Germany) were determined using commercially available enzyme-linked immunoassay kits according to the manufacturer's instructions and quality controls. All measurements were performed from frozen serum/plasma samples and in duplicate.

2.5. FATTY ACID COMPOSITION OF SERUM PHOSPHOLIPIDS

Blood was collected by participants' GPs in tubes with EDTA and without anticoagulant, and stored at -80 °C. The fatty acid composition of serum phospholipids was determined in duplicate by gas chromatography (Shimadzu GmbH, model GC 2010 plus, Duisburg, Germany, flame ionization detector [FID]) as described previously (Burak et al., 2017; Egert et al., 2018). Briefly, after Folch extraction was performed on serum samples, the phospholipid fraction was separated using a silica thin-layer chromatography plate. After scraping off the phospholipid band under ultraviolet light, the phospholipid fraction was methylated by transesterification with methanol/HCl. The fatty acids methyl esters were extracted with petroleum ether, dissolved in heptane, and injected into the gas chromatograph. Peaks of interest were identified by comparing with authentic fatty acid methyl ester standards. Selected fatty acids were expressed as a percentage of the total area by dividing the integrated area under the peak by the total area of all fatty acids. Fatty acids were also determined quantitatively from the internal standard and expressed as µmol/l serum.

2.6. DIETARY INTAKE ASSESSMENT

At FU-1, dietary intake of foods was assessed using a short and concise 8-item "cognitive health" food intake screener developed by the AgeCoDe study group. Participants were asked how often they usually consumed fresh fish (not canned), olive oil, fruits and vegetables (excluding potatoes), meat and sausages, red wine, white wine, green tea, and coffee. For each food item, options to answer were (1) "never"; (2) "less than once a week"; (3) "once a week"; (4) "several times per week"; (5) and "each day", resulting in an intake score (range 0-4) for each food item.

3 RESULTS

3.1. STUDY 1 : LOW VITAMIN D STATUS IS ASSOCIATED WITH INCIDENT ALZHEIMER'S DEMENTIA IN THE OLDEST OLD

3.1.1. INTRODUCTION

The worldwide number of elderly people is increasing, and simultaneously so is the number of people with dementia (Blennow, et al., 2006; Jicha and Carr, 2010). The research should therefore focus on modifiable risk factors, such as diet, to counteract this trend. Fat soluble vitamins with anti-oxidative properties have been linked with cognitive outcomes and may help protect against dementia risk factors (Grimm, et al., 2016). Vitamin E is the main lipid-soluble antioxidant, and its most common form is alpha-tocopherol (Grimm, et al., 2016). As compared to the different vitamin E forms, alpha-tocopherol has the highest bioavailabilty (Gropper, et al., 2009). However, studies have shown that tocotrienols have stronger antioxidant properties (Galli, et al., 2007; Nesaretnam, 2008). Vitamin E acts as a cellular membrane protector and neuro protector by counteracting oxidative stress, and fights against Aß free radicals (Hu, et al., 2013; Lin and Beal, 2006). Vitamin D contributes to neurotransmitter release, functions as a neuroprotector and fights against oxidative stress and pro-inflammatory agents (Grimm, et al., 2016). Vitamin A and beta-carotene function as antioxidants that tend to scavenge lipid peroxidation and neurotransmitter release (Grimm, et al., 2016; Lopes da Silva, et al., 2014). On the other hand, ox-LDLs may also be a peripheral marker of the severity of oxidative stress in dementia, mediating risk factors for dementia, such as atherosclerosis and CVD. They (Chang, et al., 2014; Steinberg, 2009; Toth, 2008). To date, results of observational studies are promising, but studies are few and not entirely consistent. For example, previous studies have found low blood concentrations of vitamins A, D, E, and beta-carotene in dementia participants (Grimm, et al., 2016; Lopes da Silva, et al., 2014; Sommer, et al., 2017). In contrast, increased blood ox-LDL concentrations have been observed in AD patients, however, in a small sample (n= 202) (Schrag et al., 2013). Furthermore, to our best knowledge, only two observational studies have investigated the association between ox-LDL and dementia in the elderly, reporting negative results for the whole study population (Koyama, et al., 2013; Murr, et al., 2014). We therefore examined the relationship between vitamins A

and E, and beta-carotene, with incident AD or all-cause dementia in the AgeCoDe multicenter cohort study in Germany. Furthermore, an additional case-control sample was available to investigate the associations between vitamin D and ox-LDL, and incident AD.

3.1.2. STUDY SPECIFIC METHODS

STUDY PARTICIPANTS

Vitamins A and E, and beta-carotene study sample - For the present study, we used data from participants who had available FU data from FU-3 until FU-8. We excluded participants who did not meet the initial study inclusion criteria (n= 110), died (n= 511) or dropped out before FU-3 (n= 821), resulting in a sample of 1,995 participants at FU-3. From the 1,995 participants at FU-3, we excluded participants for whom vitamin A, beta-carotene and/or vitamin E data, and/or cognitive data was not available (n= 536). We also excluded 76 participants with prevalent dementia at FU-3, resulting in a sample of n= 1,383 participants. Details on the exclusion of participants of the present study are presented in **Fig. 1**.

Vitamin D and ox-LDL study sample - Vitamin D and ox-LDL were analyzed in a case-control sub-sample (n= 401), by selecting 124 cases that were non-demented at FU-3 progressing to incident AD until FU-8, and by randomly selecting about twice as many non-demented control subjects without incident dementia until FU-8, matched to the AD dementia cases by age, sex, and education. By excluding participants for whom vitamin D and/or ox-LDL, and/or cognitive data was not available (n= 23), this case-control sample consisted of 382 participants, including 118 cases with incident AD and 264 matched controls.

CONFOUNDERS

For the present study, education was classified into three levels (low, middle, and high) based on the Comparative Analysis of Social Mobility in Industrial Nations (CASMIN) classification system. For genetic and blood biomarker analyses blood samples were drawn from each participant at the attending GP practice (Brauns and Steinmann, 1999).

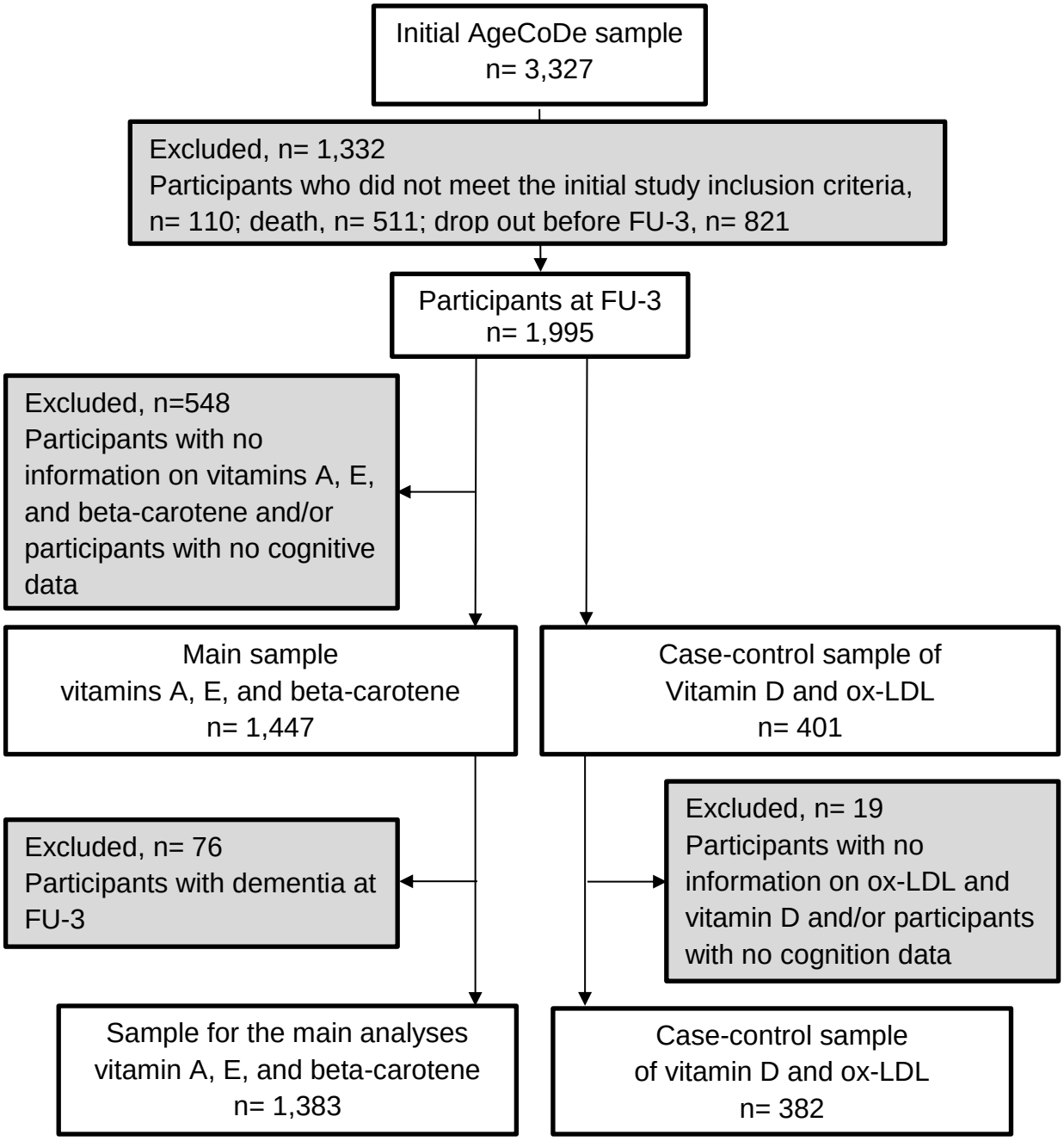

Fig. 1: Flow chart of the participants included in the analyses of study 1. Abbreviations: AgeCoDe, German Study on Ageing, Cognition and Dementia in Primary Care Patients; n, number; FU, follow up; ox-LDL, oxidized-low density lipoprotein.

APOE genotyping was performed according to standard procedures (Hixson and Vernier, 1990). Participants were grouped into those with at least one *APOE* ε4 allele and those without an ε4 allele. Body height and weight were measured at FU-3. BMI was calculated by dividing participants' weight (kilogram; kg) by the square of their height (m^2). Smoking status was assessed at the baseline visit and used as a proxy for

FU-3. Smoking was divided into three categories: never smoker, former smoker, and current smoker. Assessment of physical activity was conducted at FU-3. We constructed a modified physical activity score based on Verghese et al. (Verghese et al., 2003). Participants reported the frequency of usual engagement in each of the following six physical activities: bicycling, walking, swimming, gymnastics, chores/gardening, and a category of other physical leisure activities (e.g., bowling, jogging, or golfing) using five possible options to answer: (1) “each day”; (2) “several times per week”; (3) “once a week”; (4) “less than once a week”; and (5) “never”. For the present study, the five frequency categories were collapsed into two categories whether the participant usually engaged in one of the six activities (once a week to each day = 1) or not (less than once a week and never= 0). For each participant, these values (0 or 1) were summed up across the six activities to a total physical activity score (scoring 0-6). Serum concentrations of total cholesterol, triglycerides and creatinine (FU-3) were determined by the p- and ecobas® modular platform from the manufacturer Roche. Blood pressure was assessed at FU-3 by participants GP. Vitamin supplement intake was based on self-report. Seasonality was calculated using the date of blood drawn. Memory decline was calculated using the CERAD neuropsychological assessment battery (we applied the validated German version (Thalmann et al., 2000)) 10-item Word List Delayed Recall subtest (scoring 0-10; higher scores indicating a better memory performance). We subtracted the cognitive test data of FU-3 from the baseline measurement’s test data.

STATISTICAL ANALYSIS

Participants were grouped by cognitive status at FU-3 into cognitively normal (non-demented) participants, and participants with all-cause dementia or AD. We analyzed plasma concentrations of vitamins A, D, E, beta-carotene, and ox-LDL. Cox proportional hazard models (hazard ratios; HR, 95 % confidence interval; CI) were used to investigate the longitudinal associations between the effect of one (milligram per litre) (mg/l) increase of vitamins A and E, and beta-carotene and incident AD or all-cause dementia, from now on referred to as the main sample. In addition, Cox proportional hazard models were used to investigate the associations between the effect of one nanogram/milliliter (ng/ml) or mg/l increase of vitamin D and ox-LDL and incident AD, from now on referred as case-control sample. We tested the proportional hazard assumption using the statistical program R (cox.zph), the proportional hazard

assumption was satisfied for all. Furthermore, we investigated vitamins A, D, E, beta-carotene, and ox-LDL as continuous variables. Confounders were selected based on published literature. Nine confounders (BMI, *APOE* ε4, creatinine, total cholesterol, triglycerides, physical activity, vitamin supplement intake, systolic, and diastolic blood pressure) contained missing values. The percentages of missing values ranged from 1.6 % (vitamin supplement intake) to 20.0 % (triglycerides) in the main sample, and ranged from 2.1 % (physical activity) to 21.5 % (triglycerides) in the case-control sample. To account for potential attrition bias, multiple imputation (MI) was used by creating 10 different possible copies of the original dataset, in which the missing values were substituted by imputed values (**Table 1**). These imputed values were calculated from their predictive distribution based on the observed data (Sterne et al., 2009). Combined results of the ten created datasets were then pooled in a separate pooled dataset, to account for the uncertainty about the missing values. All models were conducted using imputed data. Models were adjusted for sociodemographic factors: age, gender, education, and *APOE* ε4 status (Model 1). Additionally to Model 1, for the lifestyle factors BMI, smoking status and physical activity, creatinine, total cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, vitamin supplement intake, and memory decline (Model 2). We included memory decline in Model 2 to account for reverse causality caused by baseline cognitive status. Vitamin D was additionally adjusted for seasonality. We investigated interactions between the vitamins and ox-LDL, and gender or *APOE* ε4 status in model 2 ($P_{interaction}$ <0.10). In addition, effect modification between beta-carotene and *APOE* ε4 in particular has previously been reported (Hu, et al., 2006; Maddock et al., 2015; Zito et al., 2013). Stratified analyses were performed according to gender status (male, or female) or *APOE* ε4 status (carrier, or non-carrier). A $P < 0.05$ was considered statistically significant. International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) Statistics for Windows (Release 23) was used to perform the analyses.

3.1.3. RESULTS

Table 1 details the study population characteristics, subdivided by study sample. The mean age was 84 years, women were slightly more represented than males, and the mean BMI was 26 kg/m^2. The *APOE* ε4 allele was present in 19.3 % or 18.6 % of the

Table 1: Characteristics of the AgeCoDe participants of study 1

	Case-control sample Vitamin D and ox-LDL n= 382	Main sample Vitamin A, beta-carotene, vitamin E n= 1,383
Age (years)	84 ± 3	84 ± 3
Female (n, %)	269 (70.4)	890 (64.4)
BMI (kg/m^2)	25.9 ± 3.8	26.0 ± 3.8
APOE ε4 allele (n, %)	71 (18.6)	267 (19.3)
Memory decline score	0.2 ± 2.1	-0.1 ± 2.1
Time to develop Alzheimer's dementia (years)	2 ± 2	3 ± 2
Time to censoring (years)	6 ± 1	5 ± 2
Blood analyses		
Vitamin A (mg/l)	0.52 ± 0.20	0.54 ± 0.23
Beta-carotene (mg/l)	0.32 (IQR: 0.22-0.46)	0.32 (IQR: 0.22-0.48)
Vitamin D (ng/ml)	10.47 (IQR: 6.03-18.37)	-
Vitamin E (mg/l)	15.52 ± 5.82	15.72 ± 6.38
Ox-LDL (mg/l)	0.15 (IQR: 0.10-0.22)	-
Creatinine (mg/dl)	0.99 (IQR: 0.82-1.22)	1.00 (IQR: 0.83-1.22)
Total cholesterol (mg/dl)	2.22 ± 0.45	2.21 ± 0.48
Triglycerides (mg/dl)	1.09 (IQR: 0.87-1.46)	1.11 (IQR: 0.87-1.49)
Education (n, %)		
Lower	264 (69.1)	809 (58.5)
Middle	92 (24.1)	410 (29.6)
High	26 (6.8)	164 (11.9)
Physical activity (n, %)		
Low (0-1)	29 (7.6)	121 (8.7)
Middle (2)	265 (69.4)	943 (68.2)
High (3-5)	88 (23.0)	319 (23.1)
Smoking (n, %)		
Never	210 (55.0)	700 (50.6)
Past	156 (40.8)	596 (43.1)
Current	16 (4.2)	87 (6.3)
Vitamin supplement intake (n, %)	22 (5.8)	83 (6.0)
Systolic blood pressure (mmHg)	135 ± 16	136 ± 16
Diastolic blood pressure (mmHg)	80 (IQR: 70-80)	80 (IQR: 70-80)

Based on imputed data. Values are means ± SD, numbers (valid percentages), or medians (interquartile range). Abbreviations: AgeCoDe, German Study on Ageing, Cognition and Dementia in Primary Care Patients; APOE ε4, apolipoprotein ε4; ox-LDL, oxidized Low Density Lipoprotein; n, number; kg, kilograms; m^2, squared meter; mg, milligrams; l, litre; ng, nanogram; ml, millilitre; dl, decilitre; mmHg, millimeter of mercury.

participants in the main sample or the case-control sample, respectively. Mean vitamin A and vitamin E concentrations were 0.54 mg/l and 15.72 mg/l, respectively. Median vitamins D, beta carotene and ox-LDL concentrations were 10.47 ng/ml, 0.32 mg/l, and 0.15 mg/l, respectively. Over approximately seven years of FU 263 participants developed dementia, of which 221 participants developed AD in the main sample.

LONGITUDINAL ASSOCIATIONS BETWEEN VITAMINS AND OX-LDL AND INCIDENT AD

Higher vitamin D concentrations were significantly associated with a lower incidence of AD (Model 1: HR= 0.97, 95 % CI 0.95; 0.99) **(Table 2)**. The association remained significant after full adjustment of confounding factors (Model 2: HR= 0.97, 95 % CI 0.95; 0.99). In addition, Vitamin D was also examined as a binary variable by using the existing reference value (i.e. ≥ 20 ng/mL) as a cut-off (Holick et al., 2011). Here we also observed that low vitamin D concentrations (present in n=305 participants) were associated with a higher risk of incident AD (Model 1: HR= 2.20, 95 % CI 1.23; 3.92 and Model 2: HR= 2.02, 95 % CI 1.10; 3.72) **(Table 2)**. We observed no significant associations between the other vitamins and ox-LDL and risk of incident AD **(Table 2)** or all-cause dementia (data not shown).

SECONDARY ANALYSES

We observed a significant interaction between beta-carotene and gender ($P_{interaction}$ = 0.009) with regard to incident AD, but not between beta-carotene and *APOE* ε4 status ($P_{interaction}$ = 0.699) **(Table 2)**. As in the literature interactions with *APOE* ε4 have been observed (Hu, et al., 2006; Maddock, et al., 2015; Zito, et al., 2013), we performed analyses stratified by gender or *APOE* ε4 status, which revealed that beta-carotene was not significantly associated with incident AD in men or women, nor in *APOE* ε4 carriers or non *APOE* ε4 carriers (all adjusted model P- values > 0.09) **(Table 3)**. For vitamins A, E, and beta-carotene, the results remained non-significant when we examined incident all-cause dementia rather than AD dementia. (data not shown).

Table 2: Longitudinal associations between blood concentrations of vitamins A, D, E, beta-carotene, and ox-LDL and incident AD over a 7-year FU period – Study 1

	Incidence of AD				P-values for interaction	
Vitamins	Model 1		Model 2		Gender	*APOE* ε4
Vitamin A, beta-carotene and vitamin E (n= 1,383)						
	HR (95 % CI)	*P*	*HR* (95 % CI)	*P*		
Vitamin A (mg/l)	1.01 (0.62; 1.97)	0.746	1.13 (0.60; 2.13)	0.705	-	-
Beta-carotene (mg/l)	0.98 (0.64; 1.50)	0.916	1.03 (0.65; 1.63)	0.901	0.009	0.699*
Vitamin E (mg/l)	1.01 (0.99; 1.03)	0.341	1.21 (0.86; 1.72)	0.276	-	-
Vitamin D and ox-LDL (n= 382)						
	HR (95 % CI)	*P*	*HR* (95 % CI)	*P*		
Vitamin D (ng/ml)	0.97 (0.95; 0.99)	0.016	0.97 (0.95; 0.99)	0.024	-	-
ox-LDL (mg/l)	1.00 (0.99; 1.00)	0.661	1.00 (0.99; 1.00)	0.154	-	-
Vitamin D deficiency						
Vitamin D, n= 305 <20 (ng/ml)	2.20 (1.23; 3.92)	0.008	2.02 (1.10; 3.72)	0.023	-	-

Based on imputed data. Abbreviations: AD= Alzheimer's dementia; *APOE* ε4, apolipoprotein ε4; CI= confidence interval; HR, hazard ratio; mg, milligrams; l, litre; ng, nanogram; ml, millilitre; ox-LDL, oxidized - low density lipoprotein
Model 1 is adjusted for age, sex, *APOE* ε4 and education.
Model 2 is adjusted as for model 1, plus BMI, physical activity and smoking, memory decline, total cholesterol, creatinine, triglycerides, systolic blood pressure and diastolic blood pressure and vitamin supplement intake.
A P-value <0.05 is considered to be statistical significant. *= interaction observed in previous studies.

Table 3: Analyses stratified by gender or *APOE* ε4 status (n= 1,383) – Study 1

	Incidence of AD			
	Model 1		Model 2	
Vitamins	HR (95 % CI)	P	HR (95 % CI)	P
By gender				
Beta-carotene (mg/l)				
Men (n= 493)	1.80 (0.92; 3.55)	0.085	1.44 (0.73; 2.87)	0.296
Women (n= 890)	0.77 (0.44; 1.35)	0.354	0.87 (0.48; 1.60)	0.661
By *APOE* ε4 status				
Beta-carotene (mg/l)				
APOE ε4 carrier (n= 267)	0.69 (0.23; 2.12)	0.520	0.36 (0.07; 1.96)	0.237
APOE ε4 non-carrier (n= 1,116)	1.08 (0.68; 1.74)	0.738	1.17 (0.73; 1.89)	0.520

Based on imputed data. Abbreviations: *APOE* ε4, apolipoprotein ε4; AD= Alzheimer's dementia; HR, hazard ratio; CI= confidence interval; mg, milligrams; l, litre.
Model 1 is adjusted for age, *APOE* ε4 (for the gender-stratified analyses) or gender (for the *APOE* ε4 stratified analyses) and education.
Model 2 is adjusted as for model 1, plus BMI, physical activity and smoking, memory decline, total cholesterol, creatinine, triglycerides, systolic blood pressure and diastolic blood pressure and vitamin supplement intake.
A P-value <0.05 is considered to be statistical significant.

3.1.4. DISCUSSION

In a longitudinal multicenter cohort study, we investigated the relationhips between vitamins A, D, E, beta-carotene, and ox-LDL with incident AD or all-cause dementia. We observed a longitudinal assocation between serum vitamin D concentrations and incident AD in the elderly.

FINDINGS IN OTHER STUDIES

Vitamin D - Our finding that a low status of vitamin D is associated with AD dementia is consistent with previous population-based longitudinal studies (Afzal et al., 2014; Annweiler et al., 2011; Feart et al., 2017; Knekt et al., 2014; Littlejohns et al., 2014; Sommer, et al., 2017). A systematic review and meta-analysis including 18,974 individuals also demonstrated that vitamin D deficiency was associated with an increased risk of incident AD (Sommer, et al., 2017). By contrast, three studies reported no association. However, two studies (Karakis, et al., 2016; Schneider, et al., 2014) were performed in slightly younger participants, and very few participants in the third study (Olsson, et al., 2017) had vitamin D concentrations below 20 ng/ml (50 nanomol per litre (nmol/l)) (Karakis, et al., 2016; Olsson, et al., 2017; Schneider, et al., 2014). To date, very few RCTs have been carried out, of which the majority failed to show an effect of vitamin D supplementation (Landel, et al., 2016). However, Mokry et al. (2016) conducted a mendelian randomization (MR) and reported that a decrease in vitamin D concentrations resulted in an increased risk for AD, which was primarily driven by rs2282679 in the gene *GC* (Mokry et al., 2016). By contrast, Kueider et al. (2016) also conducted a MR analysis and reported no association between vitamin D and global cognition (Kueider et al., 2016). Vitamin D is involved in several brain functions such as: counteracting oxidative stress and inflammation, release of neurotransmitters, calcium homeostasis, A*ß* deposition, and modulation of the immune system (Landel, et al., 2016; Sommer, et al., 2017). The vitamin D receptor, which functions as a gene regulator, is highly expressed in several areas of the brain: the cortex, hippocampus, dopamine neurons and brain nucleus (Brouwer-Brolsma and de Groot, 2015; Cui, et al., 2013; Eyles, et al., 2014; McCann and Ames, 2008). Changes in vitamin D related gene expression might induce aging and neurodegeneration (Gezen-Ak, et al., 2014). It is hypothesized that at first, Aß is able to obstruct the use of vitamin D, causing “inefficient utilization of vitamin D” (Gezen-Ak, et al., 2014). Secondly, vitamin D deficiency may

induce an accumulation of Aß due to an imbalance of calcium homeostasis, or oxidative stress (Gezen-Ak, et al., 2014). These underlying mechanisms might explain our findings.

Vitamin A - We observed that vitamin A was not associated with dementia. Six small case-control studies found significant lower levels of vitamin A in AD or all-cause dementia participants as compared to controls (Bourdel-Marchasson et al., 2001; Foy, et al., 1999; Jimenez-Jimenez, et al., 1999; Polidori and Mecocci, 2002; Raszewski, et al., 2016; Rinaldi, et al., 2003). However, participants were only age and/or sex matched, or adjustments were made for age, sex and education only. Nevertheless, our observation was confirmed by observational studies investigating the relation between vitamin A and global cognition or cognitive decline (Johnson, et al., 2013; Kang and Grodstein, 2008; Schmidt, et al., 1998).

Beta-carotene - We found that beta-carotene was not associated with dementia. Our finding is in line with the majority of studies which did not report an association with global cognition, cognitive decline or AD (Foy, et al., 1999; Johnson, et al., 2013; Kang and Grodstein, 2008; Polidori and Mecocci, 2002; Rinaldi, et al., 2003; Schippling, et al., 2000; Schmidt, et al., 1998). In contrast, others did find an association (Hu, et al., 2006; Jimenez-Jimenez, et al., 1999; von Arnim, et al., 2012). However, studies were either small, minimally adjusted for confounders, or conducted in a younger population. Furthermore, one longitudinal study also found an interaction between beta-carotene and *APOE* ε4 and reported an association between beta-carotene and cognitive decline in *APOE* ε4 carriers only (Hu, et al., 2006). We found an interaction between beta-carotene and gender on incident AD. To the best of our knowledge we are the first to report an interaction. However, stratified analyses showed a non-significant relation between beta-carotene with a decreased risk of incident AD in women, and an increased risk of incident AD in men. Other studies are needed to confirm if gender modifies the association between beta-carotene and incident AD, as no exact mechanism is known to cause this discrepancy.

Vitamine E - Our finding that vitamin E was not associated with the risk to AD or all-cause dementia is in line with previous prospective observational studies (Cherubini et al., 2005; Mangialasche et al., 2010; Mangialasche et al., 2013; Mangialasche et al.,

2012). Results of these studies revealed that total tocopherols and tocotrienols, rather than alpha-tocopherol alone, are associated with cognitive decline and AD. By contrast, observational studies have reported a relation between concentrations or dietary intake of vitamin E (alpha-tocopherol) with cognitive function, AD or cognitive impairment (Boccardi, et al., 2016). RCTs have reported mixed results as well. One RCT observed a slowing functional decline in AD patients after receiving 2000 IU per day of vitamin E (alpha-tocopherol) over 2 years of FU (Dysken et al., 2014). However, a second trial reported both lower and higher concentrations of oxidative stress in AD participants (Lloret et al., 2009).

Ox-LDL - We are one of the first studies to investigate the association between ox-LDL and dementia in a population-based study. Our finding for ox-LDL is in line with two other longitudinal studies (Koyama, et al., 2013; Murr, et al., 2014). One study was conducted in community dwelling women (mean age 82.6 years), which did not show associations with risk of dementia and risk of MCI after five years of FU (Koyama, et al., 2013), and a second study did not report a relation with the risk of all-cause dementia, AD and vascular dementia in men and women over 11 years of FU (Murr, et al., 2014). In contrast, one study did report increased blood ox-LDL concentrations in AD patients, however, in a small sample (n= 202) (Schrag, et al., 2013).

STRENGTHS AND LIMITATIONS

An important strength of our study is the longitudinal study design in the oldest old. Furthermore, we were able to investigate blood concentrations of vitamins and ox-LDL, which give a better reflection of their status in the human body as compared to dietary intake. In addition, we were able to adjust for a wide range of confounders, particularly factors that might affect the association between vitamin D and cognitive health. In addition, we were able to adjust for memory decline (prior to baseline measurement of the vitamins and ox-LDL) to account for reverse causation. We also recognize that our study has limitations. Single measurement of concentrations of vitamins in serum or plasma may not reflect the vitamin status of the body (Mangialasche, et al., 2013; Sommer, et al., 2017). Also, high oxidative stress might cause decreased concentrations of the antioxidants due to an increased demand (Ford et al., 2003). However, longitudinal studies have reported longitudinal stability of plasma vitamins D and E, and

ox-LDL (Comstock et al., 2001; Holvoet et al., 2006; Sommer, et al., 2017). Furthermore, we did not have dietary vitamins supplement data on the specific vitamins, however, we were able to adjust the associations for total vitamin supplement intake. In addition, we did not have data on sun exposure, but we were able to adjust for month of blood assessment. Our study has an observational design. Thus, even though we adjusted for multiple confounders, residual confounding might still be present. Also, a causal relationship cannot be established, but needs to be investigated further in intervention studies. We cannot rule out selection bias completely, as we selected our samples based on data availability on the vitamins, ox-LDL and cognitive health. However, we were able to investigate vitamins A, E and beta-carotene in a large sample. Furthermore, survival bias might be present as our participants were 75 years and older, which might have affected the generalizability of our study towards younger populations. On the other hand, the GP based AgeCoDe cohort is very representative for German elderly at this age range.

CONCLUSION

Vitamin D deficiency increased the risk to develop AD. Our study supports the advice for more sun exposure and vitamin D supplementation in those with vitamin D deficiency. We observed no relationship between the other vitamins and ox-LDL with development of AD or all-cause dementia, which is in line with previous observational studies.

3.2. STUDY 2: HIGHER CONCENTRATION OF EPA IS ASSOCIATED WITH A DECREASED INCIDENCE OF ALZHEIMER'S DEMENTIA IN THE OLDEST OLD

3.2.1. INTRODUCTION

Our food habits throughout our life will have a role on modulating our personal risk to dementia, including influences on dementia risk factors such as T2D and CVD (Ley et al., 2014; Ndanuko et al., 2016; Solfrizzi, et al., 2017). Regular consumption of fatty fish, for example, has been associated with slower cognitive decline (Samieri, et al., 2018). In fact, prospective observational studies investigating serum/plasma or erythrocytes PUFAs have shown beneficial effects against dementia (van der Lee, et al., 2018; Yanai, 2017). This protective effect has been primarily attributed to the long chain n-3 PUFAs, EPA and DHA (Yanai, 2017). The role of their plant-derived precursor ALA is less clear, although it is the principle dietary n-3 PUFA consumed in the typical Western diet (Geleijnse et al., 2010). ALA can be converted into EPA and DHA by elongation and desaturation, but the extent of this conversion is not clear and at best is very limited (Baker et al., 2016; Barcelo-Coblijn and Murphy, 2009). Dietary EPA and DHA are readily incorporated into cell membranes where they influence membrane function (Hooijmans and Kiliaan, 2008). Furthermore, DHA and EPA, present in the brain, have anti-inflammatory and neuronal protective properties and may help protect against dementia (Yanai, 2017). Interestingly, n-3 PUFAs metabolism has been additionally related to *APOE*, the major genetic risk factor for AD which is the most common form of dementia (Harris et al., 2014; Samieri et al., 2013b). *APOE* is the main lipoprotein in the brain, which has a key role in the transport of lipids and brain lipid metabolism (Grimm, et al., 2017). It has been hypothesized that the *APOE* ε4 genotype might modify the protective effects of n-3 PUFAs (Harris, et al., 2014; Samieri, et al., 2013b). One study reported an association between moderate to high intake of n-3 PUFAs and slower rates of cognitive decline in *APOE* ε4 carriers, but not in *APOE* ε4 non-carriers (van de Rest, et al., 2016). On the other hand, two studies investigated the modification of the association between blood concentrations of fatty acids and dementia by *APOE* ε4 status, but both studies observed no significant modification by *APOE* ε4 status.(Kroger, et al., 2009; Samieri, et al., 2008). The blood lipid contents of EPA and DHA have been widely used as biomarkers of intake and surrogates of their enrichment in cellular

membranes (Baylin and Campos, 2006). In fact, lower blood concentrations of EPA and DHA have been reported in dementia patients (de Wilde et al., 2017). Herein, the most accepted way of reporting concentrations of these fatty acids is as percentage distribution of total fatty acids in a given compartment instead of fatty acid concentration (Sergeant et al., 2016). This issue has been a matter of debate for over 20 years (Sergeant, et al., 2016), given the mathematical consideration that needs to be accounted for when expressing fatty acids concentrations as a percentage. In fact, research has shown that the relationship between fatty acids changes depending on whether they are expressed as percentage or as concentration, which is especially true for n-6 PUFAs (Sergeant, et al., 2016). These differences in expressing data might explain the contradictory results observed with PUFAs and dementia. We therefore examined prospectively the relation between serum n-3 and n-6 PUFAs with incident all-cause dementia or AD in the AgeCoDe multicenter cohort study in Germany. We examined both percentage distribution of concentrations of PUFAs and absolute concentrations of PUFAs in serum phospholipids. In addition, we investigated *APOE* ε4 status as a potential effect modifier.

3.2.2. STUDY SPECIFIC METHODS

STUDY PARTICIPANTS

For the present study, we used data from participants who attended the third FU visit (FU-3) and at least one of the additional FU visits (until FU-8). We excluded participants who did not meet the initial study inclusion criteria (n= 110), died (n= 511) and dropped out (n= 821), resulting in a sample of 1,995 participants at FU-3. From these 1,995 participants, we excluded participants for whom serum PUFAs, and/or cognitive data was not available at the FU visits. Consequently, the sample for our longitudinal analyses included 1,264 participants. Details on the exclusion of participants of the present study are presented in **Fig. 2**.

CONFOUNDERS

For the present study, education was classified into three levels (low, middle, and high) based on the CASMIN classification system (Brauns and Steinmann, 1999). For genetic and blood biomarker analyses, blood samples were drawn from each participant at the attending GP practice. *APOE* genotyping was performed according to standard

procedures (Hixson and Vernier, 1990). Participants were grouped into those with at least one *APOE* ε4 allele (homo- and heterozygous carriers; positive *APOE* ε4 status) and those without an ε4 allele (non-carriers, negative *APOE* ε4 status). Body height and weight were measured at FU-3. BMI was calculated by dividing participants' weight (kg) by the square of their height (m^2). Smoking status was assessed at the baseline visit and used as a proxy for FU-3. Smoking was divided into three categories as never smoker, former smoker, and current smoker. Assessment of physical activity was conducted at FU-3. We constructed a modified physical activity score based on Verghese et al. (Verghese, et al., 2003). Participants reported the frequency of usual engagement in each of the following six physical activities: bicycling, walking, swimming, gymnastics, chores/gardening, and a category of other physical leisure activities (e.g., bowling, jogging, or golfing) using five possible options to answer: (1) "each day"; (2)

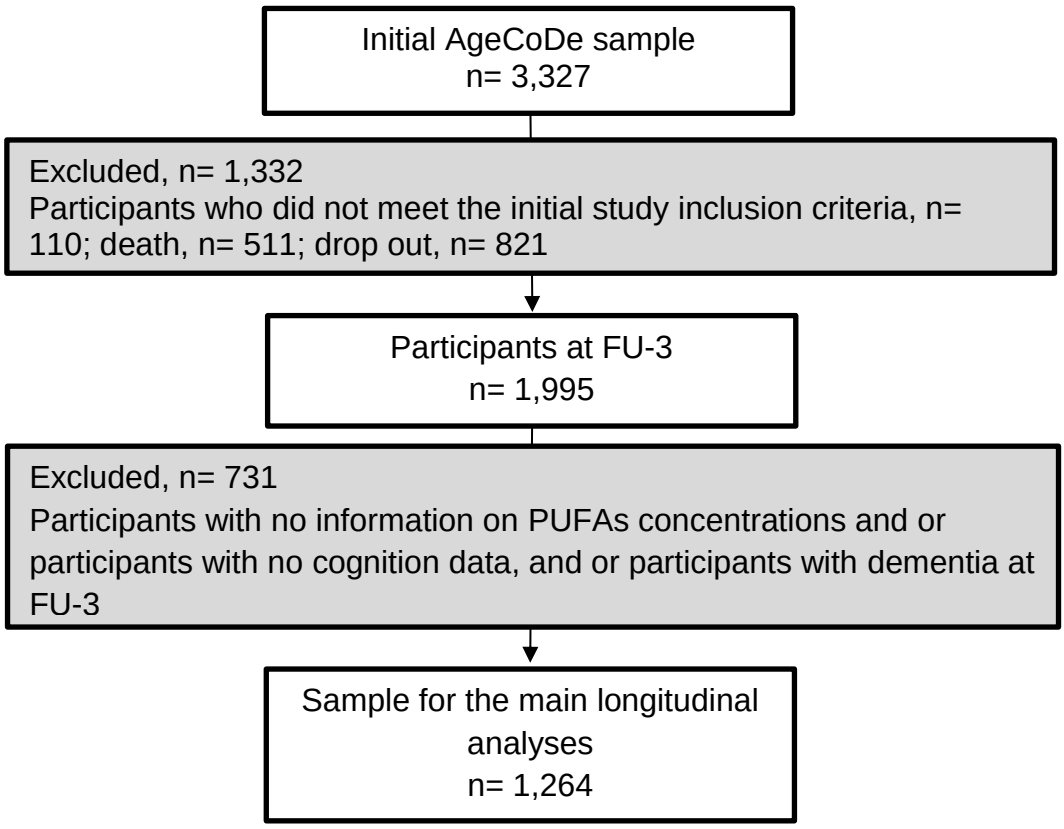

Fig. 2: Flow chart of the participants included in the analyses of study 2. Abbreviations: AgeCoDe, German Study on Ageing, Cognition and Dementia in Primary Care Patients; n, number; FU, follow up; PUFA, polyunsaturated fatty acid; AD, Alzheimer's dementia.

“several times per week”; (3) “once a week”; (4) “less than once a week”; and (5) “never”. For the present study, the five frequency categories were collapsed into two categories whether the participant usually engaged in one of the six activities (once a week to each day= 1) or not (less than once a week or never= 0). For each participant, these values (0 or 1) were summed up across the six activities to a total physical activity score (scoring 0-6). For determination of vitamin E (alpha-tocopherol), the plasma samples were deproteinized by addition of ethanol (containing apocarotenal as the internal standard, 5 µmol/L). The fat-soluble vitamin was extracted with n-hexane and analysed using normal-phase HPLC and ultraviolet detection. Serum concentration of total cholesterol (FU-3) was measured using polychromatic endpoint measurement. Serum concentrations of triglycerides (FU-3), was measured using bichromatic endpoint measurement with a Dimension Vista 1500 analyzer (Siemens Healthcare Diagnostics GmbH) (Brull et al., 2017). Memory decline was calculated using the CERAD neuropsychological assessment battery (we applied the validated German version (Thalmann, et al., 2000)) 10-item Word List Delayed Recall subtest (scoring 0-10; higher scores indicating a better memory performance). We subtracted the cognitive test data of FU-3 from the test data of the baseline measurement. Lipid lowering medication was categorized into users and non-users.

STATISTICAL ANALYSIS

Participants were grouped by cognitive status at FU-3 into non-demented participants, and participants with AD or all-cause dementia. We analyzed concentrations of ALA, EPA, DHA, LA, DGLA and AA, and percentage distribution of concentrations of these PUFAs. Cox proportional hazard models were used to investigate the longitudinal associations between the effect of 1 SD increase in n-3 and n-6 PUFAs, and incidence of AD or all-cause dementia. We tested the proportional hazard assumption using the statistical program R (cox.zph), the proportional hazard assumption was satisfied for all. Confounders were selected based on published literature. Six confounders (BMI, *APOE* ε4, vitamin E, total cholesterol, triglycerides, physical activity) contained missing values (data not shown). The percentages of missing values ranged from 2.1 % (physical activity) to 19.9 % (triglycerides) for the analysis. To account for potential attrition bias, MI was used by creating ten different possible copies of the original dataset, in which the missing values were substituted by imputed values **(Table 4)**. These imputed values

Table 4: Characteristics of the AgeCoDe participants of study 2

	Study sample n= 1,264
Age (y)	84 ± 3
Female (n, %)	812 (64.0)
BMI (kg/m^2)	25.9 ± 3.8
APOE ε4 status (n, %)	240 (19.0)
Duration to develop dementia (y)	5 ± 2
Vascular dementia at FU 3 (n, %)	-
AD at FU 3 (n, %)	-
Memory decline score	-0.1 ± 2.1
Blood analyses	
alpha-Linolenic acid (µmol/l)	10 ± 7
Eicosapentaenoic acid (µmol/l)	72 ± 50
Docosahexaenoic acid (µmol/l)	217 ± 105
Linoleic acid (µmol/l)	990 ± 406
Dihomo-γ-linolenic acid (µmol/l)	153 ± 59
Arachidonic acid (µmol/l)	618 ± 239
alpha-Linolenic acid (%)	0.17 ± 0.08
Eicosapentaenoic acid (%)	1.08 ± 0.65
Docosahexaenoic acid (%)	3.77 ± 1.10
Linoleic acid (%)	18.05 ± 2.90
Dihomo-γ-linolenic acid (%)	2.75 ± 0.66
Arachidonic acid (%)	9.14 ± 2.03
alpha -tocopherol (mg/l)	15.71 ± 6.36
Triglycerides (g/l)	1.18 (IQR: 0.93-1.39)
Total cholesterol (g/l)	2.21 ± 0.47
Education (n, %)	
Lower	734 (58.1)
Middle	375 (29.7)
High	155 (12.3)
Physical activity (n, %)	
Low (0-1)	102 (8.1)
Middle (2)	853 (67.5)
High (3-5)	309 (24.4)
Smoking (n, %)	
Never	647 (51.2)
Past	542 (42.9)
Current	75 (5.9)
Lipid lowering medication n, %)	256 (20.3)

Based on imputed data. Values are means ± SD, Values are means ± SD, numbers (valid percentages), or medians (interquartile range). Abbreviations: n= number; AgeCoDe, German Study on Ageing, Cognition and Dementia in Primary Care Patients; *APOE* ε4, apolipoprotein ε4; AD= Alzheimer's dementia; y, years; FU, follow up; kg, kilograms; m^2, squared meter; µmol, micromole; mg= milligrams; l, litre; dl= milligrams decilitre; g= grams.

were calculated from their predictive distribution based on the observed data (Sterne, et al., 2009). Combined results of the ten created datasets were then pooled in a separate pooled dataset, to account for the uncertainty about the missing values. All models were conducted using imputed data. Models were adjusted for sociodemographic factors: age, gender, education, and *APOE* ε4 status (Model 1); additionally to Model 1, for the lifestyle factors BMI, smoking status and physical activity, vitamin E, total cholesterol, triglycerides, cognitive decline, and lipid lowering medication (Model 2). We included memory decline in Model 2 to account for reverse causality caused by baseline cognitive status. We investigated interactions between *APOE* ε4 status and the n-3 and n-6 PUFAs in model 2 ($P_{interaction}$ <0.10). When significant, stratified analyses were performed according to *APOE* ε4 status (carrier, or non-carrier). A $P < 0.05$ was considered statistically significant. IBM SPSS Statistics for Windows (Release 23) was used to perform the analyses.

3.2.3. RESULTS

Table 4 details the study population characteristics, subdivided by study sample. The mean age was 84 years, women were slightly more represented than males and the mean BMI was 25.9 kg/m^2. The *APOE* ε4 allele was present in 19.0 % of the participants. Mean concentrations of ALA, EPA and DHA were 10 µmol/l, 72 µmol/l, and 217 µmol/l, respectively. Additionally, mean concentrations of LA, DGLA and AA were 990 µmol/l, 153 µmol/l, and 618 µmol/l, respectively. Over approximately seven years of FU, 233 participants developed dementia of which 190 participants developed AD.

LONGITUDINAL ASSOCIATIONS BETWEEN CONCENTRATIONS OF N-3 AND N-6 PUFAS AND INCIDENT ALL-CAUSE DEMENTIA OR AD

Higher serum phospholipid EPA concentrations were borderline significantly associated with a lower incidence of all-cause dementia (Model 1: HR= 0.86, 95 % CI 0.74; 1.01) **(Table 5)**. The association disapeared after full adjustment (Model 2: HR= 0.88, 95 % CI 0.75; 1.02). However, higher EPA concentrations were significantly associated with a lower incidence of AD in model 1 and model 2 (Model 2: HR= 0.76, 95 % CI 0.63; 0.92) **(Table 6)**. Also, higher DHA concentrations were associated with a lower incidence of AD in model 1 (HR= 0.84, 95 % CI 0.71; 0.99) but no longer in model 2 (HR= 0.86, 95 %

Table 5: Longitudinal associations between concentrations or percentage of n-3 and n-6 PUFAs and incident all-cause dementia over a 7-year FU period (n= 1,264) – Study 2

n-3 and n-6 PUFAs	Incidence of all-cause dementia				P-values for interaction
	Model 1		Model 2		*APOE* ε4
	HR (95 % CI)	*P*	*HR* (95 % CI)	*P*	
Concentrations (SD)					
alpha-Linolenic acid	0.91 (0.78; 1.06)	0.227	0.94 (0.81; 1.10)	0.427	0.052
Eicosapentaenoic acid	0.86 (0.74; 1.01)	0.057	0.88 (0.75; 1.02)	0.092	0.004
Docosahexaenoic acid	0.88 (0.77; 1.03)	0.112	0.92 (0.79; 1.07)	0.283	-
Linoleic acid	1.02 (0.90; 1.17)	0.744	1.05 (0.93; 1.19)	0.415	-
Dihomo-γ-linolenic acid	0.99 (0.86; 1.13)	0.885	1.01 (0.88; 1.17)	0.891	-
Arachidonic acid	0.97 (0.85; 1.12)	0.698	0.96 (0.84; 1.10)	0.562	0.078
Percentage (SD)					
alpha-Linolenic acid	0.92 (0.80; 1.05)	0.213	0.95 (0.82; 1.09)	0.420	-
Eicosapentaenoic acid	0.91 (0.79; 1.06)	0.216	0.93 (0.81; 1.08)	0.332	0.061
Docosahexaenoic acid	1.04 (0.91; 1.18)	0.566	1.08 (0.95; 1.23)	0.248	-
Linoleic acid	1.04 (0.91; 1.18)	0.577	1.07 (0.94; 1.22)	0.311	-
Dihomo-γ-linolenic acid	1.03 (0.90; 1.18)	0.631	1.05 (0.91; 1.21)	0.490	-
Arachidonic acid	1.02 (0.90; 1.16)	0.739	0.98 (0.85; 1.13)	0.797	-

Based on imputed data. Abbreviations: n-3= omega-3; n-6= omega; PUFA, polyunsaturated fatty acid; *APOE* ε4, apolipoprotein ε4; CI= confidence interval; HR, hazard ratio.
Model 1: age, gender, *APOE* ε4, education.
Model 2: model 1 plus BMI, physical activity, smoking, memory decline, alpha- tocopherol, triglycerides, total cholesterol and lipid lowering medication.
A P-value <0.05 is considered to be statistical significant.

Table 6: Longitudinal associations between concentrations or percentage of n-3 and n-6 PUFAs and incident AD over a 7-year FU period (n= 1,264) – Study 2

n-3 and n-6 PUFAs	Incidence of AD				P-values for interaction
	Model 1		Model 2		*APOE* ε4
	HR (95 % CI)	*P*	*HR* (95 % CI)	*P*	
Concentrations (SD)					
alpha-Linolenic acid	0.87 (0.73; 1.04)	0.136	0.90 (0.76; 1.08)	0.259	-
Eicosapentaenoic acid	0.75 (0.62; 0.91)	0.003	0.76 (0.63; 0.92)	0.006	0.021
Docosahexaenoic acid	0.84 (0.71; 0.99)	0.037	0.86 (0.73; 1.03)	0.093	-
Linoleic acid	1.05 (0.92; 1.20)	0.492	1.07 (0.95; 1.20)	0.302	-
Dihomo-γ-linolenic acid	1.01 (0.87; 1.17)	0.879	1.03 (0.88; 1.20)	0.295	-
Arachidonic acid	0.96 (0.83; 1.12)	0.636	0.94 (0.81; 1.10)	0.465	-
Percentage (SD)					
alpha-Linolenic acid	0.89 (0.76; 1.04)	0.153	0.93 (0.79; 1.08)	0.330	-
Eicosapentaenoic acid	0.83 (0.70; 0.99)	0.040	0.85 (0.72; 1.02)	0.076	-
Docosahexaenoic acid	1.04 (0.90; 1.20)	0.588	1.09 (0.94; 1.26)	0.240	-
Linoleic acid	1.09 (0.94; 1.26)	0.269	1.12 (0.96; 1.30)	0.139	-
Dihomo-γ-linolenic acid	1.08 (0.93; 1.25)	0.338	1.10 (0.94; 1.28)	0.231	-
Arachidonic acid	0.99 (0.87; 1.15)	0.987	0.96 (0.82; 1.12)	0.583	-

Based on imputed data. Abbreviations: AD= Alzheimer's dementia; n-3= omega-3; n-6= omega-6; PUFA, polyunsaturated fatty acid; *APOE* ε4, apolipoprotein ε4; CI= confidence interval; HR, hazard ratio.
Model 1: age, gender, *APOE* ε4, education.
Model 2: model 1 plus BMI, physical activity, smoking, cognitive decline, alpha- tocopherol, triglycerides, total cholesterol and lipid lowering medication.
A P-value <0.05 is considered to be statistical significant.

CI 0.73; 1.03). We observed no significant associations between the other PUFAs and incident AD or all-cause dementia **(Table 6)**.

LONGITUDINAL ASSOCIATIONS BETWEEN PROPORTIONS OF N-3 AND N-6 PUFAS AND INCIDENT ALL-CAUSE DEMENTIA OR AD

We observed in our sample that higher proportions of EPA were significantly associated with a lower incidence of AD (Model 1: HR= 0.83, 95% CI 0.70, 0.99). After adjustments for lifestyle factors, vitamin E, total cholesterol, triglycerides, cognitive decline and lipid lowering medication the association was no longer significant (Model 2: HR= 0.85, 95 % CI 0.72; 1.02) **(Table 6)**. No such associations were observed between percentage DHA or the other n-3 and n-6 PUFAs and AD or all-cause dementia **(Tables 5 and 6).**

SECUNDARY ANALYSES

We observed significant interactions between *APOE* ε4 and AA concentrations, *APOE* ε4 and ALA concentrations, *APOE* ε4 and EPA concentrations, and *APOE* ε4 and proportions of EPA **(Tables 7 and 8)**. After stratifying according to *APOE* ε4 status we observed that the relations between concentrations of AA, ALA, and proportions of EPA with incidence all-cause dementia in *APOE* ε4 carriers and non-carriers went were similar to the main analysis **(Tables 7 and 8)**. The association between higher concentrations of EPA and a decreased risk for incident all-cause dementia became stronger in *APOE* ε4 non-carriers (Model 2: HR= 0.76, 95 % CI 0.61; 0.94), but attenuated in *APOE* ε4 carriers **(Table 7)**. In addition, a similar effect was observed between higher concentrations of EPA and a decreased risk for incident AD in *APOE* ε4 non-carriers (Model 2: HR= 0.67, 95 % CI 0.52; 0.86); and the effect diluted for *APOE* ε4 carriers **(Table 7)**.

3.2.4. DISCUSSION

In a longitudinal multicenter cohort study, we investigated the prospective associations between proportions and concentrations of serum phospholipid n-3 and n-6 PUFAs and incident all-cause dementia or incident AD. We observed a longitudinal association between higher serum EPA concentrations and a decreased risk of of AD in the oldest old. In addition, stratification for *APOE* ε4 status showed that higher concentrations of EPA were associated with a decreased risk of incident all-cause dementia and AD in *APOE* ε4 non-carriers.

Table 7: Analyses stratified by *APOE* ε4 status for concentrations of n-3 and n-6 PUFAs and incident all-cause dementia or AD – Study 2

	Incidence of all-cause dementia			
	Model 1		Model 2	
n-3 and n-6 PUFAs (SD)	*HR* (95 % CI)	*P*	*HR* (95 % CI)	*P*
alpha-Linolenic acid				
APOE ε4 non-carrier (n= 1,024)	0.86 (0.71; 1.05)	0.138	0.90 (0.75; 1.09)	0.293
APOE ε4 carrier (n= 240)	1.00 (0.76; 1.32)	0.978	0.96 (0.71; 1.29)	0.764
Eicosapentaenoic acid				
APOE ε4 non-carrier (n= 1,024)	0.75 (0.61; 0.92)	0.006	0.76 (0.61; 0.94)	0.010
APOE ε4 carrier (n= 240)	1.08 (0.87; 1.33)	0.497	1.06 (0.86; 1.31)	0.592
Arachidonic acid				
APOE ε4 non-carrier (n= 1,024)	0.91 (0.76; 1.07)	0.246	0.88 (0.74; 1.05)	0.153
APOE ε4 carrier (n= 240)	1.17 (0.91; 1.49)	0.229	1.18 (0.91; 1.53)	0.212
	Incidence of AD			
	Model 1		Model 2	
n-3 PUFA (SD)	*HR* (95 % CI)	*P*	*HR* (95 % CI)	*P*
Eicosapentaenoic acid				
APOE ε4 non-carrier (n= 1,024)	0.66 (0.52; 0.85)	0.001	0.67 (0.52; 0.86)	0.002
APOE ε4 carrier (n= 240)	0.95 (0.72; 1.25)	0.705	0.92 (0.69; 1.22)	0.558

Based on imputed data. Abbreviations: AD= Alzheimer's dementia; n-3= omega-3; n-6= omega-6; PUFA, polyunsaturated fatty acid; *APOE* ε4, apolipoprotein ε4; HR, hazard ratio; CI= confidence interval; mg, milligrams; l, litre.
Model 1: age, gender and education.
Model 2: model 1 plus BMI, physical activity, smoking, memory decline, alpha- tocopherol, triglycerides, total cholesterol, and lipid lowering medication.
A P-value <0.05 is considered to be statistical significant.

Table 8: Analyses stratified by *APOE* ε4 status for proportions of Eicosapentaenoic acid PUFA and incident all-cause dementia – Study 2

	Incidence of all-cause dementia			
	Model 1		Model 2	
n-3 PUFA (SD)	*HR* (95 % CI)	*P*	*HR* (95 % CI)	*P*
Eicosapentaenoic acid				
APOE ε4 non-carrier (n= 1,024)	0.86 (0.71; 1.02)	0.086	0.87 (0.73; 1.04)	0.128
APOE ε4 carrier (n= 240)	1.07 (0.84; 1.35)	0.592	1.08 (0.85; 1.37)	0.521

Based on imputed data. Abbreviations: n-3= omega-3; PUFA, polyunsaturated fatty acid; *APOE* ε4, apolipoprotein ε4; HR, hazard ratio; CI= confidence interval; mg, milligrams; l, litre.
Model 1: age, gender, and education.
Model 2: model 1 plus BMI, physical activity, smoking, cognitive decline, alpha- tocopherol, triglycerides, total cholesterol, and lipid lowering medication.
A P-value <0.05 is considered to be statistical significant.

OMEGA-3 PUFAS

Our findings are to some extent in line with previous prospective observational studies (Ammann, et al., 2017; Cherubini, et al., 2007; Conquer, et al., 2000; Kroger, et al., 2009; Laurin, et al., 2003; Lopez, et al., 2011; Samieri, et al., 2008; Schaefer, et al., 2006; van der Lee, et al., 2018; Yamagishi, et al., 2017). A study conducted in a French multicenter cohort study observed an association between high proportions of plasma EPA and the risk of developing all-cause dementia, while we observed an association with AD and a protective trend after full adjustment with all-cause dementia (Samieri, et al., 2008). Similar to our study, the authors did not observe associations between higher proportion distributions of plasma LA, AA, ALA and DHA and all-cause dementia (Samieri, et al., 2008). In concert to our study, a longitudinal study reported no association between percentage plasma DHA (analyzed continuously) and incident all-cause dementia (Schaefer, et al., 2006). However, the authors demonstrated an association between high proportions of DHA, as compared to low proportions of DHA, and a lower risk for all-cause dementia (Schaefer, et al., 2006). We tested the associations between DHA and AD or all-cause dementia for non-linearity with a quadratic term in the model, but this was not significant. Other longitudinal studies reported an association between erythrocyte contents of DHA and EPA combined with a lower risk of all-cause dementia (Ammann, et al., 2017); or did not observe any association between high concentrations of total n-3 PUFAs, DHA or EPA measured in erythrocytes and all-cause dementia or AD (Kroger, et al., 2009). By contrast, a meta-analysis (n= 25,872), including a small sample of our cohort study, has reported an association between high proportions of plasma/serum DHA and lower risks of all-cause dementia and AD (van der Lee, et al., 2018). Probably due to lack of statistical power, we and other studies were not able to replicate this finding as our effect estimates pointed into the expected direction. Intervention studies investigating the effect of n-3 PUFAs have shown contradictonary results, as some studies did find beneficial effects of total n-3 PUFAs or EPA and DHA (Chiu et al., 2008; Eriksdotter et al., 2015; Kulzow et al., 2016; Sinn et al., 2012), while others did not (Andrieu et al., 2017; Freund-Levi et al., 2008; Geleijnse et al., 2012; Hashimoto et al., 2017; Ngandu et al., 2015; Phillips et al., 2015; Quinn et al., 2010; Soininen et al., 2017; van de Rest et al., 2008; Yurko-Mauro et al., 2010). AD is characterised by the accumulation of neurotoxic Aβ peptide in

the brain (Yanai, 2017). DHA and EPA, both present in the brain, are involved in the clearence of accumulated Aβ through IDE (Grimm, et al., 2017). In addition, PUFAs concentrations have been associated with an increase of the non-amyloidogenic processing of APP leading to an increased α-secretase-cleaved soluble APP (sAPPα) secretion, which has a neurotrophic and neuroprotective function (Yanai, 2017). Also, both PUFAs have anti-inflammatory properties, which are used to diminish inflammation in the brain, resulting in an enhancement of Aβ degradation (Grimm, et al., 2017). Furthemore, our effect differences of EPA after stratification for *APOE* ε4 status might be explained by the hypothesis that the *APOE* ε4 allel, a major risk factor for AD, has an influence on the homeostatis of the PUFAs (Barberger-Gateau et al., 2011; Grimm, et al., 2017). Previous studies have reported mixed results. Our study is in line with three other observational studies, which also observed an effect in *APOE* ε4 non-carriers only (Barberger-Gateau, et al., 2007; Huang et al., 2005; Whalley et al., 2008). On the other hand, studies have also demonstrated an association between higher concentrations of EPA or DHA with slower cognitive decline in *APOE* ε4 carriers only (Samieri et al., 2011; van de Rest, et al., 2016). *APOE* ε4 might have an influence on PUFAs in the blood flow, as it has been postulated that *APOE* ε4 interferes the metabolism of PUFAs during transport of the PUFA in the blood flow, but also when EPA and DHA tend to cross the blood-brain-barrier (Barberger-Gateau, et al., 2011; Grimm, et al., 2017). Our result may be explained by an increased vulnerability of *APOE* ε4 to dietary deficit of n-3 PUFAs, as carriers of the ε4 allele catabolize more n-3 PUFAs than non-carriers (Nock et al., 2017).

OMEGA-6 PUFAS

A limited number of studies have reported mixed results on the association between n-6 PUFAs and dementia (Heude, et al., 2003; Kalmijn, et al., 1997; Milte, et al., 2011; Morris, et al., 2003; Samieri, et al., 2008). Similar to our study, a French longitudinal study reported no associations between high proportions of LA or AA measured in plasma and incident all-cause dementia (Samieri, et al., 2008). In addition, a second study also reported no association between high dietary intake of LA and AD (Kalmijn, et al., 1997). In contrast, a longitudinal study reported an association between high dietary intake of n-6 PUFAs (i.e. including LA and AA) and a reduced risk for AD after 3.9 years of FU (Morris, et al., 2003), which one would not expect. At the time of that study, the harmful effect of n-6 PUFAs was not yet known, therefore the authors did not elaborate

on this finding. Another study also reported an association between higher proportions of total n-6 PUFAs measured in erythrocytes, but with a higher odds for cognitive decline (Heude, et al., 2003). In concert with the previous study, a case-control study reported higher proportions of erythrocyte DGLA and AA in mild cognitive impaired participants in comparison to controls (Milte, et al., 2011). In contrast to n-3 PUFAs, n-6 PUFAs have pro-inflammatory properties. The predominant n-6 PUFA is AA, which is converted to lipoxygenase or cyclooxygenase products (Schmitz and Ecker, 2008). These products have an inflammatory, atherogenic and prothrombotic functions (Schmitz and Ecker, 2008). N-3 PUFAs counteract these pro-inflammatory effects of n-6 PUFAs.

MEASUREMENT METHODS OF CONCENTRATIONS OF FATTY ACIDS

Fatty acids can be derived from serum, erythrocyte membranes, triglycerides, phospholipids or cholesterol esters, or adipose tissue (Arab, 2003; Willett, 1998). Each method has its own strenghts and limitations. In addition, multiple factors might influence assessment methods of concentrations of fatty acids and therefore should be taken into account, these include: dietary fat intake, supplement use, nutritional status, lipogenesis, oxidation or disease status (Arab, 2003). Serum fatty acid concentrations tend to reflect dietary intake of the last days, whereas fatty acids derived from erythrocyte membranes tend to reflect long-term intake (Arab, 2003). Furthermore, one should be especially cautious when interpretating proportions of fatty acids, as the proportion of one fatty acid depends on the proportion of the other fatty acids (Willett, 1998). This means that when the concentration of one fatty acid is low, it does not necessarily mean a metabolic interaction (i.e a between fatty acid interaction) has taken place (Willett, 1998). This might explain why we observed an association between absolute concentrations of EPA and AD and a borderline significant association between the proportion of concentrations of EPA and AD, because the effect of the proportions of EPA might have been attanuated by the proportions of other fatty acids. Moreover, we hypothesized that because of the proportions of EPA, we were not able to find an effect of the proportion distribution percentages of the other PUFAs including DHA on all-cause dementia or AD.

STRENGHTS AND LIMITATIONS

An important strength of our study is that we were able to measure the proportion of concentrations of PUFAs from total fatty acids, as well as absolute concentrations of

PUFAs in the oldest old. Furthermore, our study had a prospective longitudinal study design in which we could investigate the predictive value of n-3 and n-6 PUFAs in the oldest old. In addition, we were able to adjust for a wide range of important confounders, including memory decline (prior to baseline measurement of the PUFAs) to account for reverse causation. We also recognize that our study has its limitations. Our study has an observational study design, which implies that a causal relationship cannot be established and reverse causality and residual confounding cannot be fully ruled out. Reverse causality might be present as it might be that increased inflammatory processes before disease onset have led to decreased concentrations of the n-3 PUFAs in the circulation due to their function as anti-inflammatory agents (Ford, et al., 2003). Furthermore, we did not measure PUFAs profiles of other tissues (e.g., adipose tissue) or blood cells (e.g., erythrocytes), which reflect long-term fatty acid intake. Furthermore, residual confounding might still be present, although, we were able to adjust for multiple confounders. Also, our study was conducted in a German population, which limits the generalizability of our results to other ethnicities. Lastly, survival bias might be present as our participants were 75 years and older, which may also affect the generalizability to younger populations. On the other hand, the GP based AgeCoDe cohort is very representative for German elderly at this age range.

CONCLUSION

In conclusion, higher concentrations of EPA were associated with a lower incidence of AD. In addition, we observed that higher concentrations of EPA were associated with a decreased risk for both all-cause dementia and AD in *APOE* ε4 non-carriers. Furthermore, higher percentage distribution of concentrations of EPA, DHA or ALA were not associated with incidence all-cause dementia or AD. This discrepancy might be explained by the dependency on the proportions of other fatty acids included in the fatty acid assessment. Our study supports the advice to eat fatty fish regularly.

3.3. STUDY 3: PROSPECTIVE ASSOCIATIONS BETWEEN INDIVIDUAL FOODS, ALZHEIMER'S DEMENTIA AND MEMORY DECLINE IN THE ELDERLY

3.3.1. INTRODUCTION

Cognitive decline and dementia are a major cause of disability and mortality in very old adults. The most common cause of dementia worldwide is AD, which is a progressive neurodegenerative disorder, which frequency exponentially increases with age (Blennow, et al., 2006; Jicha and Markesbery, 2010). The disease is becoming a major public health concern and socioeconomic burden with an estimated global prevalence of about 107 million in 2050 (Brookmeyer et al., 2007). In order to counteract this trend, modifiable lifestyle factors, such as diet, may play a pivotal role in the prevention and treatment of cognitive decline and AD (Bell, 2005; Williams et al., 2010). In recent years, increasing interest has been devoted to the role of dietary factors as risk factors in AD and cognitive impairment (Bell, 2005). To date, no dietary approach has been conclusively proven to protect against cognitive decline (Hu, et al., 2013; Solfrizzi, et al., 2011). Moreover, results from different studies investigating the same dietary aspect have often been contradictory (Hu, et al., 2013). Nevertheless, various observational and controlled intervention studies suggest that specific nutrients, foods, or all-cause dietary patterns may be effective (Hu, et al., 2013; Mi et al., 2013; Otaegui-Arrazola et al., 2014; Parletta et al., 2013; Solfrizzi, et al., 2011; Swaminathan and Jicha, 2014). As nutrients are not consumed in isolation but as part of foods or a diet with possible synergistic or antagonistic interactions (Jacobs and Steffen, 2003), investigating foods or all-cause dietary patterns rather than individual nutrients seems to be a more promising approach. However, when information is only available for complex dietary patterns, it is not clear which of the foods or nutrients provided by the diet are most effective and thus should be especially included in diets of individuals at high risk of developing cognitive impairment or dementia. Moreover, investigating foods is of scientific and practical advantage because individual foods, or simple combinations of foods, are the units we usually consume during the day (Jacobs and Tapsell, 2007). Additionally, they are easy to understand and to implement, and they are the units most appropriate for public health purposes. Individual foods that have been inversely linked to cognitive impairment and/or dementia include fish (Cederholm, 2017; Hu, et al., 2013; Otaegui-Arrazola, et

al., 2014; Parletta, et al., 2013; Solfrizzi, et al., 2011), wine (Arntzen, et al., 2010; Otaegui-Arrazola, et al., 2014; Solfrizzi, et al., 2011), red wine in particular (Hu, et al., 2013; Parletta, et al., 2013; Solfrizzi, et al., 2011), olive oil (Berr, et al., 2009; Parletta, et al., 2013; Solfrizzi, et al., 2011), fruits (Hu, et al., 2013; Otaegui-Arrazola, et al., 2014; Parletta, et al., 2013; Solfrizzi, et al., 2011), vegetables (Hu, et al., 2013; Loef and Walach, 2012; Otaegui-Arrazola, et al., 2014; Parletta, et al., 2013; Solfrizzi, et al., 2011), coffee (Hu, et al., 2013; Liu, et al., 2016), and green tea (Hu, et al., 2013; Lim et al., 2013; Mandel and Youdim, 2012; Noguchi-Shinohara, et al., 2014). By contrast, high meat intake, especially of red and processed meat products, has been shown by some studies to be positively associated with (Albanese, et al., 2009; Giem et al., 1993; Otaegui-Arrazola, et al., 2014), and by other studies to not be associated with (Barberger-Gateau et al., 2002) with risk of dementia. However, to our knowledge, no study has investigated the association of such “cognitive health” foods with cognitive decline or dementia in a German population. In addition, compared to a number of studies on food intake and global cognition, the relationships between individual foods and memory decline are understudied. These associations, however, are of interest as memory is greatly affected in AD. Also, memory tests are more sensitive than global cognition tests (Morris et al., 1999). Furthermore, recent evidence suggests that the impact of foods on cognitive health outcomes may be modified by *APOE* ε4 (Barberger-Gateau, et al., 2011; Bunce et al., 2004; Huang, et al., 2005; Martinez-Lapiscina et al., 2014; Morris, 2016; Nock, et al., 2017; Otaegui-Arrazola, et al., 2014; Smith and Blumenthal, 2016; van de Rest, et al., 2016), a major risk factor for dementia (Tudorache et al., 2017; Wisniewski and Frangione, 1992; Zhao et al., 2018) or by gender (Arab et al., 2011; Araujo et al., 2016; Lassek and Gaulin, 2011). Although, such interactions are biologically plausible, and could lead to personalized nutrition strategies, they are rarely studied systematically. Joint modeling (JM), i.e. the simultaneous analysis of survival (time-to-event) and repeated-measures (longitudinal) data of related processes (Tsiatis, 2004), is a method which is increasingly used in medical research (Asar et al., 2015; Ibrahim et al., 2010; Sudell et al., 2016), especially when the data contains nonrandom dropouts, which is common in a study including elderly participants. To the best of our knowledge, JM has not been used to investigate the association between food intake, cognitive decline, and the incidence of dementia in the elderly. The

aim of the present study was to utilize JM to investigate whether dietary intake of commonly eaten and supposed “cognitive healthy” foods was longitudinally associated with the incidence of AD or memory decline in participants of the AgeCoDe cohort. In addition, we analyzed whether these associations were modified by gender or *APOE* ε4 status.

3.3.2. STUDY SPECIFIC METHODS

STUDY PARTICIPANTS

For the present study, we used data from participants who attended the first FU visit (FU-1) because information on food intake was collected at FU-1. Of the 3,327 participants investigated at baseline, we excluded participants with FU-1 informant-based information only (n= 482) and participants that were lost to follow up before the FU-1 visit (n= 25), resulting in a sample of 2,820 participants at FU-1. From these 2,820 participants, we further excluded in total 198 participants who, at baseline, received a study diagnosis of dementia (n= 42) or were aged below 75 years (n= 37; falsely classified as 75 years or older in the study selection process) as well as those participants with dementia at FU-1 (n= 107), and/or those participants whose dietary intake data (n= 20) and/or data on depression (n= 17), and/or cognitive data (data on CERAD; n= 15) was not available at FU-1. Consequently, the sample of non-demented participants with complete cognitive test data at FU-1 included 2,622 participants. The exclusion of participants of the present study is shown in a flow chart **(Fig. 3).**

CONFOUNDERS

For the present study, education was classified into three levels (low, middle, and high) based on the CASMIN classification system (Brauns and Steinmann, 1999). For genetic and blood biomarker analyses blood samples were drawn from each participant at the attending GP practice. Leucocyte DNA was isolated using the Qiagen blood isolation kit according to the manufacturer´s instructions (Qiagen, Hilden, Germany). *APOE* genotyping was performed according to standard procedures (Hixson and Vernier, 1990). Participants were grouped into those with at least one *APOE* ε4 allele (homo- and heterozygous carriers; positive *APOE* ε4 status) and those without an ε4 allele (non-carriers, negative *APOE* ε4 status). Height and weight measured at FU-3 were used as

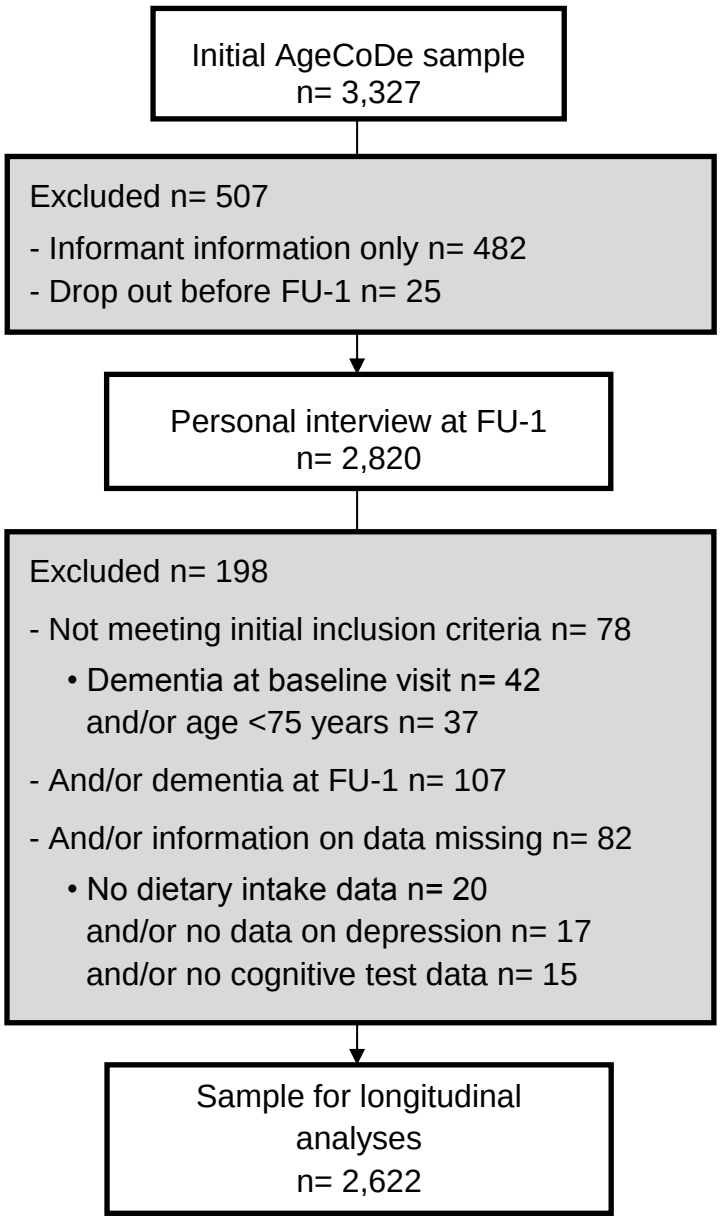

Fig. 3: Flow chart of the participants included in the analyses of study 3. Abbreviations: AgeCoDe, German Study on Aging, Cognition and Dementia in Primary Care Patients; n, number; FU, follow up.

a proxy for height and weight at FU-1. BMI was calculated by dividing participant's weight (kg) by square of their height (m^2). Smoking status was assessed at the baseline visit and used as a proxy for FU-1. Smoking was divided into three categories as never smoker, former smoker, and current smoker. Assessment of physical activity was evaluated at FU-1 based on Verghese et al. with small modifications (Verghese, et al., 2003). In brief, participants reported the frequency of usual engagement in each of the six physical activities: bicycling, walking, swimming, gymnastics, chores/gardening, and

a category of other physical leisure activities (e.g., bowling, jogging, or golfing) using five possible options to answer: (1) “each day”; (2) “several times per week”; (3) “once a week”; (4) “less than once a week”; and (5) “never”. For the present study, the five frequency categories whether the participant usually engaged in one of the six physical activities were collapsed into three categories with the following scoring: “each day” and “several times per week” = 2; “once a week” = 1; and “less than once a week” and “never” = 0. For each participant, these values (0, 1, or 2) were summed up across the six activities to give a total physical activity score (range 0-12). Depressive symptoms were assessed by using the short, 15-item version of the GDS (Sheikh et al., 1991), with a cut-off point of 6 or more used to indicate depressive symptomatology (S. and Birkner, 1999). As regards comorbidities, we used a modified score of the Charlson comorbidity index (CCI) (Charlson et al., 1987) as a proxy for disease status. The diseases included in our modified CCI score based on GP record information and comprised: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, rheumatism, diabetes, liver disease, and chronic kidney disease. All diseases were coded whether the disease was present or not (yes = 1; no = 0), with chronic kidney disease counting double according to the original CCI score. For each participant, these values (0 or 1) were summed up across the eight diseases resulting in our total modified CCI score (range 0-9).

STATISTICAL ANALYSIS

Participant characteristics at FU-1 were cross-sectionally analyzed for the total population and stratified by gender and *APOE* ε4 status. Differences in participant characteristics between men and women or between *APOE* ε4 carriers and non-carriers were examined using Student´s t-tests for continuous variables and Chi-square tests for categorical variables. JM (Asar, et al., 2015) of survival data (with time-to-event dichotomous variable “incidence of AD” as the response variable) and longitudinal data (with the continuous variable “memory decline” as the response variable) was used to investigate the longitudinal associations between intake of foods and incidence of AD together with memory decline. JM combines a Cox proportional hazards sub-model and a linear-mixed-effects repeated-measures sub-model by linking the respective random effect terms, thereby accounting for incomplete observed time-varying covariate information and possible informative dropout. For the linear-mixed-effects model part of

the analyses, participant-specific random intercept terms and random time slopes were incorporated into the models. To examine whether the intake of the individual foods modified memory over time, i.e., velocity, we included interaction terms between each individual food and time in the fixed-effects structure. Results of JM are expressed in terms of hazard ratios (for time-to-event submodels, with 95 % confidence intervals) and coefficient estimates (for linear mixed-effects submodels, with 95 % confidence intervals). Confounders were selected based on published literature. Five confounders (weight, *APOE* ε4 status, physical activity, hypercholesterolemia, and the modified CCI) contained missing values (data not shown). The percentages of missing values ranged from 0.2 % (weight) to 3.6 % (*APOE* ε4 status and modified CCI). To account for potential attrition bias, MI was used by creating ten different possible copies of the original dataset, in which the missing values were substituted by imputed values **(Table 9)**. These imputed values were calculated from their predictive distribution based on the observed data (Sterne, et al., 2009). Combined results of the created ten datasets were then pooled in a separate pooled dataset, to account for the uncertainty about the missing values. All models were run using imputed data. Models were adjusted for sociodemographic factors: age, gender, BMI, education, and *APOE* ε4 status (model 1); or additionally to model 1, for the lifestyle factors smoking status and physical activity, depression, hypercholesterolemia, and a modified CCI score (model 2). Moreover, to account for participants´ cognitive status at FU-1, the linear mixed model included the CERAD memory FU-1 score as the first repeated measure. We aimed to investigate effect modification by *APOE* ε4 status and gender. We tested for significant effect modification of the longitudinal associations between individual foods and all outcome variables by *APOE* ε4 status and gender, by including a multiplicative interaction term (food intake frequency x gender x time, or food intake frequency x *APOE ε4* status x time) in model 2. In the case of a significant interaction term ($P < 0.10$) for the AD sub-model and/or the memory decline sub-model of the JM, we stratified the analysis by *APOE* ε4 status or gender to reveal the strength and direction of the associations in the individual subgroups. *P* values are two-sided, and $P < 0.05$ was considered statistically significant. SPSS Statistics for Windows Release 21, IBM Corporation, Armonk, NY, USA) was used for descriptive analyses at FU-1; R.3.0.1 under R studio was used for the longitudinal JM analyses.

3.3.3. RESULTS

PARTICIPANT CHARACTERISTICS

Participant characteristics are presented for the total study population (81.2 ± 3.4 years, 65.3 % women, 4.5 ± 2.8 years to develop AD) as well as by gender and *APOE ε4* status **(Table 9)**. As compared to men, women were older (81.3 vs. 80.9 years, *P* = 0.001), had lower BMI (25.7 vs. 26.1 kg/m^2, *P* = 0.003), lower physical activity (*P* = 0.048), lower educational level (*P* < 0.001), lower tendency to smoke (*P* < 0.001), more often prevalent depression (12.7 % vs. 8.8 %, *P* = 0.002), and less often comorbidities (*P*< 0.001) than men, but higher CERAD memory score (73.0 vs. 69.3, *P* < 0.001) and more years to censoring (6.0 vs. 5.7, *P*= 0.047) than men. As compared to *APOE* ε4 non-carriers **(Table 9)**, *APOE* ε4 carriers had a lower BMI (25.6 vs. 25.9 kg/m^2, *P* = 0.048), and hypercholesterolemia (57.5 % vs. 52.7 %, *P* = 0.014), together with lower CERAD memory scores (69.4 vs. 72.3, *P* <0.001) and fewer years to censoring (5.6 vs. 6.0 years, *P* = 0.021). Over the 10-year FU, in the total study population (n = 2,622), 418 participants developed AD. Stratified by gender, 107 men and 311 women developed AD, whereas stratified *by APOE ε4* status, 126 *APOE* ε4 carriers and 292 *APOE* ε4 non-carriers developed AD over the period of 10 years. Food intake frequencies of the study participants are presented for the total population as well as by gender and *APOE* ε4 status **(Table 10)**. Food intake frequencies differed between men and women, with women reporting a more frequent consumption of fruits and vegetables, and men reporting a more frequent consumption of fresh fish, olive oil, meat and sausages, red wine, white wine and green tea **(Table 10)**. Food intake frequencies between *APOE* ε4 carriers and *APOE* ε4 non-carriers did not differ significantly for any food item **(Table 10)**.

LONGITUDINAL ASSOCIATIONS BETWEEN FOOD INTAKE AND INCIDENT AD OR MEMORY DECLINE IN JM

In the JM of AD and memory decline **(Table 11)**, higher red wine intake was significantly associated with lower incidence of AD in both model 1 and model 2 (model 2: HR= 0.92, 95 % CI 0.85; 0.99). No significant associations between higher intakes of the individual foods and AD and memory decline were observed in these JM. Furthermore, additional

Table 9: Characteristics of the AgeCoDe participants of study 3

	Total Population (n = 2,622)	Men (n = 910)	Women (n = 1,712)	*APOE* ε4 carriers (n = 551)	*APOE* ε4 non-carriers (n = 2,071)
Age (years)	81.2 ± 3.4	80.9 ± 3.4*	81.3 ± 3.4*	80.9 ± 3.3*	81.2 ± 3.5*
Female (n, %)	1,712 (65.3)	-	-	358 (65.1)	1,354 (65.3)
Body Mass Index (kg/m^2)	25.9 ± 3.3	26.1 ± 2.8*	25.7 ± 3.5*	25.6 ± 3.1*	25.9 ± 3.4*
APOE ε4 status (n, %)	551 (21.0)	193 (21.2)	358 (20.9)	-	-
Education (n, %)					
Low	1,594 (60.8)	483 (53.1)*	1111 (64.9)*	327 (59.3)	1,267(61.2)
Middle	723 (27.6)	220 (24.2)*	503 (29.4)*	168 (30.5)	555 (26.8)
High	305 (11.6)	207 (22.7)*	98 (5.7)*	56 (10.2)	249 (12.0)
Physical activity (n, %)					
Low (0 ≥ 3)	833 (31.8)	277 (30.4)*	556 (32.5)*	161 (29.2)	672 (32.5)
Middle (3 ≤ 5)	897 (34.2)	296 (32.5)*	601 (35.1)*	204 (37.0)	693 (33.5)
High (5–11)	892 (34.0)	337 (37.0)*	555 (32.4)*	186 (33.8)	706 (34.0)
Smoking (n, %)					
Never	1,307 (49.8)	178 (19.6)*	1,129 (66.0)*	277 (50.3)	1,030 (49.7)
Past	1,125 (42.9)	662 (72.7)*	463 (27.0)*	229 (41.5)	896 (43.3)
Current	190 (7.3)	70 (7.7)*	120 (7.0)*	45 (8.2)	145 (7.0)
Hypercholesterolemia (n, %)	1,408 (53.7)	446 (49.0)	962 (56.2)	317 (57.5)*	1,091 (52.7)*
Depression ((n, %)	298 (11.4)	80 (8.8)*	218 (12.7)*	67 (12.1)	231 (11.2)
Modified CCI score (n, %)					
Score 0–2	1,866 (71.2)	585 (64.3)*	1281 (74.8)*	408 (74.1)	1,458 (70.4)
Score 3–4	666 (25.4)	284 (31.2)*	382 (22.3)*	124 (22.5)	542 (26.2)
Score 5–6	90 (3.4)	41 (4.5)*	49 (2.9)*	19 (3.4)	71 (3.4)
CERAD memory test	71.7 ± 13.0	69.3 ± 12.8*	73.0 ± 13.0*	69.4 ± 13.6*	72.3 ± 12.8*
Time to develop AD (years)	4.5 ± 2.8	4.2 ± 2.7	4.6 ± 2.8	4.2 ± 2.7	4.6 ± 2.8
Time to censoring (years)	5.9 ± 3.3	5.7 ± 3.3*	6.0 ± 3.3*	5.6 ± 3.3*	6.0 ± 3.3*

Based on imputed data. Values are means (± SD) or numbers (valid %). Abbreviations: AgeCoDe, German Study on Aging, Cognition and Dementia in Primary Care Patients; AD, Alzheimer´s dementia; *APOE* ε4, apolipoprotein E ε4; CCI, Charlson comorbidity index; MCI, mild cognitive impairment; CERAD; Consortium to Establish a Registry for Alzheimer's Disease; kg, kilograms; m^2, squared meter. *****= significant difference between men and women or *APOE* ε4 carriers or non-carriers.

Table 10: Food intake frequencies (%) in participants of the AgeCoDe cohort – Study 3

	Total	Men	Women	*APOE* ε4 carriers	*APOE* ε4 non-carriers
	n= 2,622	n= 910	n= 1,712	n= 551	n= 2,071
Fruits and vegetables [a]					
Never	0.3	**0.4**	**0.2**	0.2	0.3
<1 time/week	0.2	**0.3**	**0.1**	-	0.2
1 time/week	0.5	**1.0**	**0.2**	0.4	0.5
Several times/week	14.8	**18.5**	**12.9**	17.1	14.2
Every day	84.2	**79.8**	**86.6**	82.4	84.7
Fresh fish					
Never	7.2	**6.7**	**7.5**	6.7	7.3
<1 time/week	30.0	**26.6**	**31.8**	31.2	29.6
1 time/week	44.9	**49.0**	**42.7**	42.3	45.6
Several times/week	17.8	**17.4**	**18.0**	19.6	17.3
Every day	0.2	**0.3**	**0.1**	0.2	0.1
Olive oil					
Never	36.3	**32.1**	**38.6**	38.3	35.2
<1 time/week	12.2	**13.0**	**11.9**	10.3	12.5
1 time/week	8.2	**7.7**	**8.5**	9.1	7.8
Several times/week	32.2	**35.8**	**30.2**	32.7	31.5
Every day	11.1	**11.4**	**10.9**	9.6	13.0
Meat and sausages[a]					
Never	1.1	**0.7**	**1.3**	1.5	1.0
<1 time/week	2.6	**1.0**	**3.4**	2.7	2.5
1 time/week	8.5	**3.5**	**11.2**	9.6	8.2
Several times/week	51.3	**45.9**	**54.1**	49.9	51.6
Every day	36.6	**48.9**	**30.1**	36.3	36.7
Red wine					
Never	52.2	**38.6**	**59.4**	52.3	52.1
<1 time/week	20.4	**22.0**	**19.6**	21.4	20.2
1 time/week	9.2	**11.3**	**8.1**	9.1	9.3
Several times/week	10.7	**16.7**	**7.5**	9.8	10.9
Every day	7.5	**11.4**	**5.4**	7.4	7.5
White wine					
Not at all	64.4	**51.4**	**71.3**	61.9	65.1
<1 time/week	20.6	**25.3**	**18.2**	22.0	20.3
1 time/week	6.1	**9.6**	**4.3**	7.3	5.8
Several times/week	7.0	**11.1**	**4.8**	6.9	7.0
Every day	1.9	**2.6**	**1.5**	2.0	1.8

Table 10 *Continued*

	Total	Men	Women	*APOE* ε4 carriers	*APOE* ε4 non-carriers
	n= 2,622	n= 910	n= 1,712	n= 551	n= 2,071
Coffee					
Never	13.2	13.0	13.3	13.1	13.2
<1 time/week	5.2	5.9	4.8	4.2	5.5
1 time/week	3.4	3.8	3.1	3.1	3.5
Several times/week	6.6	7.3	6.3	6.2	6.7
Every day	71.6	70.0	72.5	73.5	71.1
Green tea					
Never	67.7	**71.1**	**65.9**	69.3	67.3
<1 time/week	12.6	**12.0**	**12.9**	11.1	12.9
1 time/week	5.0	**3.2**	**6.0**	4.4	5.2
Several times/week	8.2	**5.8**	**9.5**	7.8	8.4
Every day	6.4	**7.9**	**5.6**	7.4	6.2

Data are valued percentages. Abbreviations: AgeCoDe, German Study on Aging, Cognition and Dementia in Primary Care Patients; *APOE* ε4, apolipoprotein E ε4 allele. [a] After collapsing categories to have at least n= 5 per category, chi-square tests revealed significant differences in the frequency (percentages are bolded) of dietary intakes for fruits and vegetables, fresh fish, olive oil, meat and sausages, red wine, white wine and green tea between men and women only. P <0.05 was considered statistically significant.

adjustment for food combinations, excluding the food under investigation, did not change the results (data not shown).We found evidence for effect modification of the association between intake of red wine and incident AD by gender, as well as of the association between intakes of fruits and vegetables, red wine, meat and sausages, and white wine and incident AD by *APOE* ε4 status **(Table 11)**. In addition, we found evidence for effect modification of the association between intakes of olive oil and white wine and memory decline by gender, and between coffee intake and memory decline by *APOE* ε4 status **(Table 11)**. We performed stratified analyses of JM of AD and memory decline only when there was evidence for effect modification ($P_{\text{interaction}} < 0.10$) by gender or *APOE* ε4 status **(Tables 11 and 12)**. Stratified by gender **(Table 12,** data for model 1 not shown**)**, higher red wine intake was associated with a lower incidence of AD among men (model 2: HR= 0.82, 95 % CI 0.74; 0.92), whereas higher red wine intake was associated with a higher incidence of AD among women (model 2: HR= 1.15, 95 % CI 1.00; 1.32). In

Table 11: Longitudinal joint modeling associations between food intake and incident AD and memory decline over a 10-year follow-up period (n= 2,622) – Study 3

	Incident AD and memory decline				P-values for interaction	
	Model 1		Model 2		Gender	*APOE* ε4
Incident AD	HR (95 % CI)	*P*	HR (95 % CI)	*P*		
Fruits and vegetables	1.04 (0.78; 1.39)	0.786	1.08 (0.80; 1.46)	0.609	-	0.085
Fresh fish	0.95 (0.84; 1.07)	0.375	0.98 (0.87; 1.11)	0.754	-	-
Olive oil	0.98 (0.91; 1.05)	0.497	1.00 (0.93; 1.07)	0.969	-	-
Meat and sausages	1.08 (0.94; 1.25)	0.270	1.09 (0.94; 1.26)	0.236	-	0.083
Red wine	0.91 (0.84; 0.98)	0.018	0.92 (0.85; 0.99)	0.045	0.001	-
White wine	0.97 (0.88; 1.08)	0.645	1.00 (0.91; 1.12)	0.875	-	0.074
Coffee	0.96 (0.90; 1.03)	0.240	0.97 (0.90; 1.04)	0.338	-	-
Green tea	0.91 (0.84; 0.99)	0.039	0.94 (0.86; 1.02)	0.129	-	-
Memory decline	B (95 % CI)	*P*	B (95 % CI)	*P*		
Fruits and vegetables	0.10 (-0.13; 0.34)	0.386	0.10 (−0.14; 0.33)	0.408	-	-
Fresh fish	-0.03 (-0.14; 0.08)	0.602	−0.03 (−0.14; 0.08)	0.610	-	-
Olive oil	-0.03 (-0.09; 0.04)	0.385	−0.03 (−0.09; 0.04)	0.388	0.064	-
Meat and sausages	0.01 (-0.12; 0.13)	0.893	0.01 (−0.11; 0.14)	0.845	-	-
Red wine	-0.04 (-0.11; 0.03)	0.308	−0.04 (−0.11; 0.03)	0.302	-	-
White wine	-0.03 (-0.12; 0.06)	0.520	−0.03 (−0.12; 0.06)	0.494	0.085	-
Coffee	-0.02 (-0.08; 0.05)	0.148	−0.02 (−0.08; 0.05)	0.241	-	0.056
Green tea	0.02 (-0.06; 0.09)	0.676	0.02 (−0.06; 0.09)	0.681	-	-

Based on imputed data. Abbreviations: AD, Alzheimer's dementia; *APOE* ε4, apolipoprotein ε4, CI= confidence interval; HR, hazard ratio; B, beta.
Model 1: age, gender, apolipoprotein ε4, Body Mass Index, and education.
Model 2: model 1 plus smoking status, physical activity score, depression, hypercholesterolemia, and a modified CCI score. A P-value <0.05 is considered to be statistical significant.

Table 12: Analyses stratified by gender or *APOE* ε4 status for food intake and incident AD or memory decline (n= 2,622) – Study 3

Food intake	Incidence of AD (Model 2)		Memory decline (Model 2)	
	HR (95 % CI)	*P*	*B* (95 % CI)	*P*
By gender				
Olive oil				
Men (n= 910)			0.06 (−0.05; 0.16)	0.285
Women (n= 1,712)			−0.08 (−0.16; 0.01)	0.065
Red wine				
Men (n= 910)	0.82 (0.74; 0.92)	<0.001		
Women (n= 1,712)	1.15 (1.00; 1.32)	0.044		
White wine				
Men (n= 910)			0.04 (−0.09; 0.17)	0.562
Women (n= 1,712)			−0.13 (−0.26; 0.00)	0.052
By APOE ε4 status				
Fruits and vegetables				
APOE ε4 carrier (n= 552)	1.29 (0.73; 2.27)	0.388		
APOE ε4 non-carrier (n= 2,070)	1.17 (0.88; 1.55)	0.287		
Meat and sausages				
APOE ε4 carrier (n= 552)	1.13 (0.90; 1.42)	0.293		
APOE ε4 non-carrier (n= 2,070)	1.04 (0.87; 1.22)	0.615		
White wine				
APOE ε4 carrier (n= 552))	1.21 (1.01; 1.46)	0.044		
APOE ε4 non-carrier (n= 2,070)	0.93 (0.82; 1.06)	0.245		
Coffee				
APOE ε4 carrier (n= 552)			0.11 (−0.06; 0.29)	0.202
APOE ε4 non-carrier (n= 2,070)			−0.04 (−0.11; 0.02)	0.211

Based on imputed data. Abbreviations: AD, Alzheimer´s dementia; *APOE* ε4, apolipoprotein E ε4 allele; HR, hazard ratio; JM, joint modelling. Model 2 was adjusted for age, Body Mass Index, education, smoking status, physical activity score, depression, hypercholesterolemia, modified physical comorbidity score and *APOE* ε4 status (for the gender-stratified analyses) or gender (for the *APOE* ε4 stratified analyses). $P < 0.05$ was considered statistically significant.

addition, a borderline significant association was found between higher olive oil and white wine intake and rapidity of memory decline in women (model 2: -0.13, 95 % CI -0.26; 0.00, and -0.08, 95 % CI -0.16; 0.01, respectively). Stratified by *APOE ε4* status

(**Table 12,** data for model 1 not shown), higher white wine intake was associated with a higher incidence of AD among *APOE* ε4 carriers (HR= 1.21, 95 % CI 1.01; 1.46, for model 2), but not in non-carriers. No significant stratified associations were observed between higher fruits and vegetables or meat and sausages intakes and incident AD, and higher coffee intake and memory decline.

3.3.4. DISCUSSION

To our knowledge, our study is the first to investigate the association between dietary food intake and incident AD and memory decline in a German population. Overall, we found that higher red wine intake was associated with lower incidence of AD over a 10-year FU. Interestingly, these and various other associations between intakes of foods (especially red wine and white wine) and incident AD or memory decline were modified by gender or APOE ε4 status.

Red wine and white wine - Red wine, more than white wine, was consumed at least once per week by about 40 % of men and 20 % of women in our sample. We found that higher red wine intake was associated with a lower incidence of AD. However, stratified analyses revealed that this was only true among men, in women we found an increased risk for incident AD instead. Consistent with this, we also found an association between higher white wine intake and a more rapid memory decline in women. Epidemiological studies suggest that moderate consumption of red wine may prevent or slow age-related neurodegenerative diseases (Arntzen, et al., 2010; Caruana et al., 2016; Vasanthi et al., 2012). Red wine has been frequently studied with regard to cognitive decline because red grapes are one of the richest sources of polyphenols, such as resveratrol, quercetin, and catechins, that may counteract cognitive decline and AD in a multi-target manner (Basli et al., 2012; Caruana, et al., 2016; Granzotto and Zatta, 2014). However, it is not clear if the protective effect of red wine intake can be attributed to these nutrients, or whether it is related to alcohol intake in general. For example, Weyerer et al. (2011) observed an association between light to moderate alcohol intake (regardless of type of alcoholic beverages) and a decreased risk for incident AD. Our findings could thus be ascribed to the alcohol content of red and white wine. Whereas in several epidemiological studies light-to-moderate drinking of alcoholic beverages has been

shown to be protective against cognitive decline and AD (Peters et al., 2008), higher daily intakes or abuse of alcohol have also been shown to be detrimental for brain function due to a U-shaped dose-response relationship (Beydoun, et al., 2014; Zuccala et al., 2001). Furthermore, higher white wine intake was associated with an increased risk of AD among *APOE* ε4 carriers. These findings are in line with two literature reviews concluding that the protective effect of moderate wine consumption is more likely among *APOE* ε4 non-carriers (Panza et al., 2012; Peters, et al., 2008).

Coffee - In our German study population, higher coffee intake was not associated with memory decline or incident AD despite an indication for effect modification by *APOE* ε4 status regarding memory decline. Coffee consumption may affect cognitive functions due to antioxidant, anti-inflammatory, or neuroprotective properties of phytochemicals found in coffee, including significant amounts of chlorogenic acid and caffeine (Dall'Igna et al., 2007; Higdon and Frei, 2006; Panza, et al., 2015; Shukitt-Hale et al., 2013). In line with our findings, a recent meta-analysis of eleven prospective studies did not find an association between coffee consumption (measured continuously) and measures of cognitive decline. However, a reduced risk for AD of high versus low intakes of coffee was reported (Liu, et al., 2016). To our knowledge, only two studies Investigated effect modification by *APOE* ε4 status for the risk of AD or dementia related to coffee, both studies found no significant P values for interaction (Eskelinen et al., 2009; Lindsay et al., 2002). Eskelinen et al. (2009) reported an association between moderate coffee consumption and a lower risk for dementia in both *APOE* ε4 carriers and non-carriers.

Olive oil - Olive oil is not as common in the German diet as it is in the diet of Mediterranean countries, with only about 50 % of our sample consuming it at least once per week. We observed no association between high olive oil intake and incident AD or memory decline. If anything, there was a trend towards higher olive oil consumption to be related with stronger memory decline in women, contrary to expectations. Berr et al. (2009) showed that intensive olive oil intake was associated with lower odds of cognitive deficit in visual memory and verbal fluency and decline in visual memory. However, most participants had a moderate to intensive consumption. In addition, the PREDIMED RCT observed that participants who were given the Mediterranean diet supplemented with extra-virgin olive oil showed better cognitive function than those given the control diet.

However, no associations were found for most cognitive domains (Martinez-Lapiscina, et al., 2013). Compared to the n-3 PUFAs DHA and EPA present in fish oil that play a pivotal role in brain functions (Zhang, et al., 2016), oleic acid, linoleic acid, and palmitic acid present in olive oil do not have specific roles in brain function.

Fruits and vegetables - Fruits and vegetables have been widely studied in relation to global cognitive and memory decline (Loef and Walach, 2012; Miller et al., 2017; Yusufov et al., 2017). We observed no associations between higher fruit and vegetable intake and our assessed outcomes. This is in line with a systematic review of cohort studies, reporting that those studies that analyzed fruits and vegetables combined, did not find an association with global cognition, while studies analyzing fruits and vegetables separately found an inverse association with vegetables only, indicating that evidence for a protective role of fruit consumption in global cognition is insufficient (Loef and Walach, 2012).

Meat and sausages - Meat and sausage products have not been widely studied with regard to cognitive decline. In our study, we did not observe an association between higher meat and sausages intake and incident AD or memory decline. Although, we observed an interaction with *APOE* ε4, possibly indicating that *APOE* ε4 carriers with a higher intake of meat and sausages are at increased risk for AD. Individual studies have investigated the influence of high meat intake, especially of red and processed meat products, on cognitive decline, either individually or as part of an “unhealthy” dietary pattern; some studies found a positive association (Albanese, et al., 2009; Giem, et al., 1993; Granic, et al., 2016; Otaegui-Arrazola, et al., 2014), while others found no association (Barberger-Gateau, et al., 2002) with cognitive decline. Concerns with regard to meat products are mainly related to the SAFA in animal fats as well as the heme iron in red meat, which are both risk factors for vascular disease (Fang et al., 2015; Otaegui-Arrazola, et al., 2014). Otherwise, meat provides high-quality protein (Jakobsen, et al., 2011) and other essential nutrients and functional components (Azhar, et al., 2013) with possible benefits for cognitive functioning.

Fresh fish - We did not find a significant association between fresh fish intake and either incident AD or memory decline. The consumption of seafood and fish, rich in brain-protective nutrients, including n-3 PUFAs (Fotuhi et al., 2009), has been

repeatedly associated with better cognitive function and reduced cognitive decline or lower incidence of dementia, including AD (Cederholm, 2017; Daiello et al., 2015; Salem et al., 2015). Possible reasons that we did not observe a significant association between fresh fish intake and either incident AD and memory decline in our study could be that in Germany about one third of consumed fish is freshwater fish, providing no meaningful amounts of n-3 PUFAs as compared to sea fish. Moreover, when assessing “fresh fish” only, we might not have captured all sources of fish intake.

Green tea - In contrast to our study, other cohort studies in elderly Asian adults have reported less cognitive decline with higher green tea intake (Ng et al., 2008; Noguchi-Shinohara, et al., 2014). Studies show that green tea is rich in antioxidant, anti-inflammatory, and neuroprotective phytochemicals such as flavonoids, catechins (Mandel et al., 2012; Venkatesan, et al., 2015), and caffeine (Dall'Igna, et al., 2007; Dietz and Dekker, 2017; Panza, et al., 2015). In our study higher green tea intake was not significantly associated with incident AD or memory decline. This opposite finding in our German cohort, where green tea is not a traditional, but a modern “health food”, may be explained by differing metabolic responses to green tea in Asian and Caucasian individuals due to differing ethnic and genetic backgrounds (Rains et al., 2011).

STRENGTHS AND LIMITATIONS

Our study has several important strengths. The first is the large multi-center GP-based sample that allowed the investigation of individuals across Germany and over the long observation period of 10 years. Second, standardized assessments of cognitive function were performed every 18 months, allowing for the analysis of decline trajectories and for the early detection of incident cases with dementia. Third, most effects hold true after adjusting for a range of important confounders. Fourth, we made use of the JM statistical technique to make optimal use of the available information on repeated CERAD memory measures and incident AD, with memory decline being linked to AD. An important strength of analyzing these outcomes in JM simultaneously is to increase precision, as observed in previous studies (Asar, et al., 2015; Ibrahim, et al., 2010; Sudell, et al., 2016). Furthermore, inclusion of dropout time into the model may help to account for unbiased estimates of cognitive decline in the presence of missing data and inclusion of the information of longitudinal cognitive assessments may also help to address

potentially informative censoring in the survival part of the model (Asar, et al., 2015). On the other hand, our study also has limitations. Most importantly, we were limited to the eight predefined food groups included in the cognitive health screener as we were not able to assess dietary food intake using a more extensive food frequency questionnaire. In addition, some promising food groups in relation to cognitive health, such as green leafy vegetables, berries, and fatty fish, could not be assessed as they were collapsed into one ‘fruits and vegetables’ group or one ‘fresh fish’ group. Finally, we cannot fully exclude some reverse causation bias due to changes in dietary habits some time before the onset of dementia. However, the fact that results remained virtually identical for red wine intake after excluding subjects with MCI (HR= 0.92 vs HR= 0.93) made such a reverse causation bias less likely. Given the long build-up of AD pathology, longitudinal dietary assessments starting in mid-life would be needed to address this issue. Moreover, dietary assessment by our food intake screener may have been subject to measurement error and bias: systematic error because we were not able to adjust for total energy intake; recall bias because participants may not have accurately remembered their food intakes; non-differential misclassification possibly leading to bias towards the null (Rothman, 2012); and selection or survival bias because we investigated elderly participants, increasing the likelihood that cognitively normal individuals with comorbidities in an advanced stage were too sick to be enrolled in the AgeCoDe study at baseline or died before the age of 75 years. However, similar short food intake screeners have been shown to be valid for assessing intake of specific food items in older adults (Schroder et al., 2011; Volkert and Schrader, 2013). In addition, these screeners reduce the burden for respondents and interviewers and provide a reasonably accurate ranking of intake, similar to that of a full-length dietary questionnaire (Block et al., 2000). While the methodological limitations of our food intake screener may have introduced noise into the resulting data, this does not compromise the significance of the main and interaction effects we found. Furthermore, based on the results observed in previous studies (Araujo, et al., 2016; Martinez-Lapiscina, et al., 2013; Morris, et al., 2006; Topiwala et al., 2017), we expected small effect sizes in the associations between dietary food intake and outcomes of cognitive decline. A limitation of the analysis strategy used here is that it did not enforce strict type I error control via the application of correction procedures for multiple testing. However, all individual foods

studied here had some prior evidence for being associated with dementia, and were not studied in a shotgun manner.

CONCLUSION

In conclusion, we found no evidence that the individual foods studied were protective against memory decline and AD, with the exception of red wine, which reduced the risk for AD only in men, while increasing it in women. Women appear to be more susceptible to the detrimental effects of alcohol in general, as they experienced also a steeper memory decline with higher white wine intake. We also found some evidence for effect modification by *APOE* ε4, with hazard ratios for incident AD being consistently higher in *APOE* ε4 carriers for several food items studied. This should motivate further studies regarding effect modification in nutritional epidemiology, as a step towards personalized dietary recommendations in old age.

4 GENERAL DISCUSSION

4.1. AIM AND MAIN FINDINGS

The main objective of this thesis was to investigate the role of nutrition on AD, all-cause dementia, and memory decline. To assess the relations between nutrition with cognitive health outcomes, we made use of nutrients, individual foods, and food groups. The presented studies were all conducted in a large population-based German prospective cohort study consisting of elderly participants aged 75 years and older.

The first aim was to examine the associations of vitamins and ox-LDL with AD and all-cause dementia in the oldest old (**chapter 3.1**). In this study, we were interested in fat-soluble vitamins: vitamin A, beta-carotene, vitamin D, and vitamin E. In addition, we were interested in a potential oxidative stress marker: ox-LDL. These nutritional compounds play important roles in the field of cognitive health. However, we only found an association between vitamin D and the risk of AD. Lower continuous concentration of vitamin D as well as vitamin D deficiency (<20 ng/mL) were associated with an increased risk of incident AD.

The second aim of this thesis was to investigate the association between n-3 and n-6 PUFAs and AD or all-cause dementia in the oldest old (**chapter 3.2**). We analyzed the n-3 PUFAs ALA, EPA, DHA and the n-6 PUFAs LA, DGLA, and AA as percentage distributions of concentrations and as serum phospholipid concentrations. We observed that serum phospholipid concentrations of EPA were associated with a decreased incidence of AD, but not with all-cause dementia. In contrast, percentage distributions of concentrations of EPA were associated with a decreased incidence of AD, but the associations were only borderline significant. In addition, we observed that after stratification by *APOE* ε4 status, higher concentrations of EPA were associated with a decreased risk of both incident all-cause dementia and AD in *APOE* ε4 non-carriers.

The third aim was to assess the relation between individual foods and food groups with AD and memory decline in the elderly (**chapter 3.3**). Nutrition was assessed through a short and concise 8-item “cognitive health” food intake screener, which included frequencies of dietary intake of olive oil, fruits and vegetables, meat and sausages, red

wine, white wine, green tea, and coffee. We only observed significant associations for red wine and white wine intake. We found that red wine intake reduced the risk of AD, which after stratification was only true for men. Hence, we demonstrated in women that red wine intake was associated with an increased risk of incident AD. Furthermore, we reported that after stratification in women, white wine intake was associated with a more pronounced memory decline. Also, we observed that white wine intake was associated with an increased risk of incident AD in *APOE* ε4 carriers only.

4.2. CONTRIBUTION OF THE STUDIES TO THE FIELD

All three studies included in this thesis contributed to the current body of evidence of cognitive health, where concentrations of vitamin D, the PUFA EPA and red wine intake have been found to be associated with better cognitive health.

Vitamin D - We hypothesized that higher concentrations of vitamin D would be associated with a decreased risk of incident AD, as vitamin D fullfills various protective roles in the brain in the oldest old. Indeed, we demonstrated that higher concentrations of vitamin D was related to a decreased risk of incident AD. We also reported that vitamin D deficiency was associated with an increased risk of AD. Previous studies have mostly investigated the effect of vitamin D deficiency with regard to AD, but the body of evidence is inconsistent. Our study aligns with a large systematic review and meta-analysis and a large longitudinal study in an elderly population, which reported an association between vitamin D deficiency and an increased risk of incident AD (Feart, et al., 2017; Sommer, et al., 2017). By contrast, three large longitudinal studies did not observe an association, however, participants were younger (aged 60 to 70) as compared to our study population (Karakis, et al., 2016; Olsson, et al., 2017; Schneider, et al., 2014). Moreover, evidence from RCTs is very limited and findings have been inconsistent (Landel, et al., 2016). In addition, contradictory evidence from MR studies has also been reported (Kueider, et al., 2016; Mokry, et al., 2016).

Vitamins A,E, beta-carotene, and ox-LDL - Based on previous observational studies, we anticipated that we might not find associations between concentrations of vitamin A, beta-carotene, vitamin E, and ox-LDL, and incident AD. Unfortunately, in our large

longitudinal study sample we were not able to demonstrate an association between all vitamins and a decreased incidence of AD, and between ox-LDL and an increased risk of AD. In fact, the effect estimates for vitamin A and vitamin E went in the opposite direction, and the effect estimates of beta-carotene and ox-LDL hinted towards no effect. For vitamin A and beta-carotene, heterogeneous results have previously been reported. However, our null results are in line with observational studies which did not find an association with global cognition, cognitive decline or AD (Foy, et al., 1999; Johnson, et al., 2013; Kang and Grodstein, 2008; Polidori and Mecocci, 2002; Rinaldi, et al., 2003; Schippling, et al., 2000; Schmidt, et al., 1998). In addition, evidence from observational studies on whether vitamin E as alpha-tocopherol or as a group (total tocopherols and total tocotrienols) is associated with a decreased incidence of AD remains unclear (Boccardi, et al., 2016). As compared to our study, longitudinal studies also did not demonstrate a relation between alpha-tocopherol with incident AD, but the studies were able to show associations between total tocopherols and total tocotrienols and a decreased incidence of AD (Boccardi, et al., 2016). Furthermore, ox-LDL is known for its role in cardiovascular diseases, functioning as a prooxidant and promoting inflammation, but evidence from a limited number of longitudinal studies which examined its relation with the risk of all-cause dementia, AD, or vascular dementia, is in line with our null result (Koyama, et al., 2013; Murr, et al., 2014).

EPA - According to our expectations, we were able to demonstrate that serum phospholipid concentrations of EPA were associated with a decreased incidence of AD. The association with all-cause dementia did not reach significance but the effect of EPA pointed towards the expected direction. We would have expected similar results with concentrations, but this was not the case. However, the effect estimates hinted towards the expected directions. We suggested that this result might have been caused by the fact that the proportion distribution of EPA depends on the proportion distribution of other fatty acids, which probably might have decreased the proportion of EPA. Albeit, we were not the first observational study to demonstrate no association with incident all-cause dementia. For example, a longitudinal study investigating EPA measured in erythrocytes did not observe an association with all-cause dementia or AD (Kroger, et al., 2009). Others observed an effect for total n-3 PUFAs only (Cherubini, et al., 2007; Yamagishi, et al., 2017). RCTs investigating n-3 PUFAs have reported heterogeneous

results (Chiu, et al., 2008; Eriksdotter, et al., 2015; Freund-Levi, et al., 2008; Geleijnse, et al., 2012; Hashimoto, et al., 2017; Kulzow, et al., 2016; Phillips, et al., 2015; Quinn, et al., 2010; Sinn, et al., 2012; van de Rest, et al., 2008; Yurko-Mauro, et al., 2010). For example, a recent RCT carried out in the oldest old did not observe an effect of a multinutrient supplement including n-3 PUFAs on global cognitive function (Baleztena, et al., 2018). Interestingly, most RCTs have reported an effect of n-3 PUFAs on superior memory test performance (Abubakari et al., 2014). There is a strong mechanistic relation between *APOE* ε4 and PUFAs. We were able to report that higher concentrations of EPA were associated with a decreased incidence of all-cause dementia and AD in *APOE* ε4 non-carriers. However, in *APOE* ε4 carriers the effect estimates were closer to one. It should be noted that the sample size of *APOE* ε4 carriers was small, however, our result does hint that *APOE* ε4 interferes the effect of EPA. As mentioned previously, other studies have reported mixed findings. However, *APOE* ε4 might have an influence on PUFAs in the blood flow, as it has been postulated that *APOE* ε4 interferes the metabolism of PUFAs during transport of the PUFA in the blood flow (Barberger-Gateau, et al., 2011; Grimm, et al., 2017).

DHA, ALA, LA, DGLA and AA - For the other n-3 and n-6 PUFAs, it was not completely surprising that we did not find an observational association with incident all-cause dementia or AD as several previous individual longitudinal studies also failed to report associations (Kroger, et al., 2009; Samieri, et al., 2008; Schaefer, et al., 2006). In contrast, evidence from a large pooled analysis did confirm that higher concentrations of DHA were associated with a decreased incident of all-cause dementia or AD (van der Lee, et al., 2018). Our null results might be a result of a lack of power as the effect estimates of the n-3 and n-6 PUFAs did point into the expected directions. As reported above, evidence from RCTs on n-3 fatty PUFAs and cognitive health has not yet demonstrated a consistent association between n-3 PUFAs with cognitive health outcomes.

Wine intake - We demonstrated that red wine intake was associated with a decreased risk of incident AD, which we expected. Indeed, an umbrella review of systematic reviews has reported that light to moderate alcohol consumption was associated with a decreased risk of AD and all-cause dementia (Ilomaki, et al., 2015). Furthermore, large

longitudinal studies including middle-aged adults (aged 40 to 60) or elderly (aged 70 to 81) have consistently shown that red wine intake or total alcohol beverage intake were associated with superior cognitive function test performance, slower cognitive decline, and slower memory decline (Arntzen, et al., 2010; Hassing, 2018; Nooyens et al., 2014; Stampfer et al., 2005). It was striking that both red wine and white wine intake were not associated with memory decline in our study and that our effect estimates pointed towards a rapid memory decline. In addition, after stratification by gender, the rapid memory decline was observed in women but not in men. A previous large longitudinal study in women only reported an association with slower memory decline (Stampfer, et al., 2005). In addition, we observed that in *APOE* ε4 carriers, white wine intake was associated with an increased risk of incident AD, which also was unexpected. To the best of our knowledge, no study has examined the interaction between white wine and *APOE* ε4. Therefore, our findings should be taken with caution as due to the high amount of polyphenols, in particular in red wine, one would expect an association between wine intake and slower memory decline or a decreased risk of incident AD.

Other food intake - It was rather disappointing to report no (significant) association between the other six food groups or foods and AD or memory decline. However, the effect estimates of fresh fish, meat and sausages, coffee and green tea intake hinted towards the expected directions. This might be because of power issues, as mostly meta-analyses or pooled analyses have demonstrated that higher fish intake was associated with a lower risk of incident AD or slower memory decline (Samieri, et al., 2018; Zhang, et al., 2016). The same explanation might be true for the associations between higher coffee intake and AD and higher green tea intake with memory decline (Liu, et al., 2016; Liu, et al., 2017). In addition, the term ‘fresh fish’ might have introduced noise, as it is primarily fatty fish (rich in n-3 PUFAs) that has been associated with brain health and no other kinds of fish (e.g. white fish). However, our results are aligned with meta-analyses which showed that coffee and green tea intake were not associated with all-cause dementia (Liu, et al., 2016; Liu, et al., 2017). Additionally, previous studies which examined red meat intake and all-cause dementia have reported inconclusive results. A large longitudinal study also reported no association between higher meat intake and incident all-cause dementia (Giem, et al., 1993), but a second large study did report a relation (Albanese, et al., 2009). It came as a surprise that the effects of fruits

and vegetables intake and olive oil intake on incident AD and/or memory decline did not hint towards the expected direction. This was surprising, as all three are rich in antioxidants or have anti-inflammatory compounds, and approximately 80 % of participants included in our study reported consumption of fruits and vegetables every day. An explanation for our null finding might be that small effects are usually observed in nutrition research, therefore more power and more variation is needed to observe a strong (significant) effect. Indeed, at present, previous large systematic reviews including meta-analyses have demonstrated an association between fruits and vegetables combined and a decreased risk of incident AD or cognitive decline (Jiang, et al., 2017; Wu, et al., 2017b). Furthermore, olive oil is the key food item of the Mediterranean diet, however, not widely consumed in Germany. Nearly 50 percent of our study population did not or rarely consume olive oil, which might primarily explain why our analyses did not reveal associations with decreased incidence of AD or slower memory decline. Moreover, previous large studies and a RCT have demonstrated a relation between higher olive intake and both outcomes (Berr, et al., 2009; Shakersain, et al., 2018; Valls-Pedret, et al., 2015).

4.3. METHODOLOGICAL CONSIDERATIONS

STUDY DESIGN

The AgeCoDe study is a large population-based longitudinal observational study which included participants aged 75 years and older. A strength to only include this age group is that we were able to assess the association between nutrition with cognitive health outcomes in the elderly or oldest old. As the world population is growing older it is important to investigate which role nutrition can play in disease prevention and to improve the quality of cognitive health in older age. A particular strength of the AgeCoDe study is that we were able to examine the associations between nutritional factors and incident AD or all-cause dementia and memory decline up to 10 years of FU.

Several challenges need to be acknowledged when investigating the elderly or the oldest old. At first, the elderly are a very vulnerable group. Due to aging, the uptake of nutritional compounds decreases (Granic et al., 2018), but also the transportation systems of nutritional compounds in the human body become impaired leading to

decreased concentrations of the compounds in the circulation and also in the cells (Hooijmans and Kiliaan, 2008). In addition, due to age-related diseases such as AD or T2D, there is an increased demand for antioxidants and anti-inflammatory agents to counteract oxidative stress and inflammation, which in turn leads to a decreased concentration of these compounds in the circulation (Ford, et al., 2003). On the other hand, due to changes (i.e. usually a reduction) in physical activity, the energy requirement for elderly decreases, which makes it even more important for the elderly to consume nutrient-dense foods (Granic, et al., 2018). If elderly would maintain their adherence to a healthy diet and regularly vary the intake of nutrient rich foods, they would be able to meet the increased demand. However, this is often not the case. In fact, this age group has the highest risk of malnutrition (Granic, et al., 2018). For example, we observed that approximately 80 % of our vitamin D and ox-LDL sample was vitamin D deficient. Other studies also reported a low status of vitamin D or B vitamins in the oldest old (Granic, et al., 2018). Furthermore, the elderly or the oldest old can be a healthy or active group or they can be a group with multiple diseases, which make the overall group very heterogeneous (Granic, et al., 2018). For example, in the AgeCoDe study no participant was completely free of diseases, but we were able to account for this by adjusting for chronic diseases.

General limitations that need to be acknowledged when investigating a particular age group and not the whole lifespan is the possible presence of selection or survival bias, in particular when additional selections are made. For example, we additionally selected participants on the basis of their available information on nutrition and cognitive health outcomes. Albeit, we did not further exclude individuals who did not have data on potential confounders, but used MI to estimate the missing values. Also, the inclusion of elderly participants at baseline increases the likelihood that individuals with comorbidities in an advanced stage were too sick to be enrolled in a study or died before the age of inclusion. The exclusion of these individuals might underestimate the associations under study.

Loss-to-follow up is a general problem of cohort studies irrespective of participant’s age (Rothman, 2012). In the elderly, this might be caused by disease status or death. For example, in our studies, a comparison of participant characteristics of participants

included in study 3.1., 3.2. and 3.3. showed that participants included in studies 3.1. and 3.2. were more physically active, hinting to survival bias, and the time to develop AD was shorter as compared to study 3.3. On the other hand, *APOE* ε4 status, gender, education and smoking were similar. Furthermore, generalizability towards younger or older study populations, depending on which age range has been chosen, might be affected due to the selective inclusion criteria of participants. Also, the inclusion of a homogeneous ethnicity, for example only whites, limits the generalizability to other non-white populations. In addition, although large epidemiological studies have a wide range of demographic, lifestyle or disease variables available, residual confounding might still be present. This might be due to unmeasured variables or due to measurement error within available variables (Rothman, 2012). However, one can partly account for residual confounding, due to missing variables, by using proxy variables. For example, in the AgeCoDe study, data on sun exposure and detailed vitamin supplementation was not available, therefore we used month of blood sampling and general vitamin supplementation as a proxy. At last, observational studies cannot report causal relationships. As compared to longitudinal designs, cross-sectional studies are primarily prone to reverse causation, but it might also be present in longitudinal study designs. For all three studies we were able to prospectively investigate the role of nutrition in relation to cognitive health outcomes, however, intervention studies are needed to examine causality.

NUTRITION ASSESSMENT

Nutritional biomarkers - Nutritional biomarkers are sensitive to intake, reliable and objective (Hu, 2008). However, it is not always feasible in large epidemiological studies to assess nutrient intake by biomarkers. As compared to dietary questionnaires biomarkers can be expensive (e.g. DLW method) to implement on a large scale. In addition, methods can be a major burden on the study participants, for example, the collection of 24-hour urine samples. Furthermore, biomarkers can be sensitive to, for example, supplement use, nutritional status, aging, and hormones. Also, often only individual measurement of concentrations of nutrients are taken (e.g. for financial reasons) which may not always reflect the nutrient status of the body. Although, longitudinal studies have reported longitudinal stability of nutrients measured in blood concentrations (Comstock, et al., 2001; Holvoet, et al., 2006; Sommer, et al., 2017).

Accurate dietary assessment in the elderly is a challenge. According to Volkert et al. (2013) this age group has a (1) reduced capacity to deal with stress, (2) has physical limitations such as visual impairment, hearing problems and writing difficulties, (3) has mental impairment such as a reduced short-term memory, cognitive decline, and limited attention, and (4) the individuals may not prepare the food themselves (Volkert and Schrader, 2013). Overall, observational studies use the same dietary assessment tools such as a FFQ, diet history or multiple 24h-recall in the elderly and adults (Volkert and Schrader, 2013). This is not a problem as long as the elderly do not have the aforementioned impairments or at least not to a large extent. However, most elderly do (Volkert and Schrader, 2013). This may lead to participation drop-out and a decrease in the validity of the dietary assessment (Maynard and Blane, 2009). Despite the limitations of nutritional biomarkers, challenges in the assessment of dietary intake in the elderly indicate that nutritional biomarkers are a useful tool for the assessment of nutrition in the elderly to avoid bias by measurement error. Moreover, a limitation of nutrient intake assessment is that it does not take into account the biological mechanisms after dietary intake, which biomarkers to a certain extend do.

Food intake - As aforementioned, accurate dietary assessment in the elderly is a challenge, particularly with the use of extensive dietary intake assessment methods. Therefore, either the use of the assessment tool might need to be altered, for example, including breaks during the assessment or to use a short questionnaire instead (de Vries et al., 2009; Volkert and Schrader, 2013). However, not only is dietary intake measured by extensive dietary assessment methods prone to measurement error in the elderly, it is a challenge for all ages. Recall bias might be present because participants may not accurately remembered and consequently underreport their food intakes (Rothman, 2012). However, one should be especially cautious when interpreting dietary intake in elderly. As the occurrence of malnutrition is common in the elderly, and it may be that the reported low intake is actually accurate (Volkert and Schrader, 2013). In addition, non-differential misclassification may be present, as measurement errors for dietary intake are not related to the disease, or vice versa the diagnosis of AD or all-cause dementia is not related to dietary intake, possibly leading to bias towards the null (Rothman, 2012).

A short questionnaire may reduce the burden for participants and provide a reasonably accurate ranking of intake, similar to that of a full-length FFQ (Block, et al., 2000). However, it is important that the questionnaire covers the whole diet in order to account for possible systematic error. At FU-1 of the AgeCoDe study, an 8-item “cognitive health” food intake screener, which included frequency of dietary intake was implemented. This was quite unfortunate as the 8-items did not cover the whole diet. Therefore, we were not able to completely account for systematic error as we lacked data on grams per day required to calculate and adjust for total energy intake. However, additional adjustment for other individual foods or food groups in the screener did not affect our results. Also, promising food groups in relation to cognitive health, such as green leafy vegetables and berries, could not be assessed as they were collapsed into one ‘fruits and vegetables’ group. Similarly fatty fish, was included in the ‘fresh fish’ group. This may have created noise, which could explain our null results. Previous studies have also made use of short food screeners (Schroder, et al., 2011; Volkert and Schrader, 2013). Schröder et al. (2011) compared a 14-point Mediterranean Diet Adherence Screener (MEDAS) with a 137-item semi-quantitative Food Frequency Questionnaire, and reported a moderate correlation and absolute agreement between the two assessment methods (r =0.52, Intra Class Coefficient= 0.51) (Schroder, et al., 2011). Consequently, the authors assessed the relation between the Mediterranean diet, measured by the MEDAS screener, with 10-year CHD risk and observed that a higher adherence to the Mediterranean diet was associated with a lower incidence of CHD, which had been shown previously using the FFQ (Schroder, et al., 2011). Thus, although a food screener has considerable limitations, it might be a valuable dietary assessment tool for the elderly.

NUTRIENTS OR FOODS?

Nutrients - Once we consume foods, they break into smaller particles. Nutrients fulfill a variety of functions either beneficial or detrimental for our well-being. Therefore, it is important to analyze nutrition on this ‘micro’ level to increase the understanding of the function of nutrients in relation to disease outcomes (Willett, 1998). However, when analyzing individual nutrients, it is important to take into account other nutrients which interact with the nutrient under study or which are synergists of the nutrient under study (e.g. vitamin C when examining iron) (Hu, 2002). However, nutrients can be highly

correlated with one another, which provides difficulty in adjusting for other nutrients due to multicollinearity or reduction of the independent effect of the nutrient under study when adjusting for another nutrient (Hu, 2002). Furthermore, small effects of individual nutrients are often observed which may be hard to detect, primarily in smaller sample sizes (Hu, 2002). Also, very often large variability is needed to detect an effect of the nutrient on the health outcome, as mostly the effect of nutrients is found at the lower or the higher end (Willett, 1998). In addition, the overall diet of the participants also might confound the association between the nutrient and the disease outcome (Hu, 2002). For example, n-3 PUFAs have been associated with higher adherence to the AHEI, which is a diet high in fruits, vegetables, and whole grain intakes (Akbaraly et al., 2018). These foods may independently be associated with the disease outcome, but adjustment for these foods would not completely eliminate confounding due to their interaction effect (Hu, 2002). Despite the aforementioned challenges, it is of interest to conduct nutrient analysis as it is the ground work for nutrient based intervention studies. Primarily vulnerable groups, such as the elderly, may benefit from nutrient supplementation if causal relationships could be established from RCTs, as malnutrition is common in this group.

Foods - Investigating foods is of scientific and practical advantage because individual foods, or combinations of foods, are the units we usually consume during the day (Jacobs and Tapsell, 2007). Furthermore, as aforementioned, nutrients within a food are known to interact, therefore it is key to also investigate individual foods in relation to health outcomes (Hu, 2002). However, as with nutrient research, it is important to take the effect of other foods into account in the investigation. For example, the beneficial health effect of fruit and vegetable intake might be caused by a low intake of fried food, red meat, and sweets and pastries. Therefore, if possible, a sensitivity analysis adjusting for these foods is recommended to examine the independent association between the individual food and the health outcome. An advantage of investigating individual foods in relation to health outcomes is that the results can be directly used for food intervention studies and food based dietary guidelines can be easily adjusted according to new insights. However, it is a challenge to conduct double-blind RCTs in nutrition research and not all foods (e.g. wine intake) can easily be further investigated in RCTs, due to ethical reasons. As stated earlier, it is of interest to collaborate with genetic departments

to find genes that could substitute the nutritional exposure and examine a possible causal relationship with MR (VanderWeele et al., 2014). For example, total alcohol intake has been investigated through MR in relation to CVD (Holmes et al., 2014).

As mentioned in the introduction of this thesis, many factors have been previously investigated in relation to cognitive health outcomes (Alzheimer's Association, 2016; Byers and Yaffe, 2011). As dementia is a multifactorial disease and to minimize residual confounding, it is of interest to include these sociodemographic factors including *APOE* ε4, lifestyle factors (e.g. physical activity and smoking), cardiometabolic health factors (e.g. cholesterol), and chronic diseases (e.g. DM) in the analysis.

4.4. FUTURE RESEARCH PERSPECTIVES

NUTRIENTS

Vitamins - We reported that vitamin D is an important nutritional factor as higher concentrations were associated with a decreased risk and vitamin D deficiency was associated with an increased risk of AD, respectively, in the oldest old. Due to aging, absorption of vitamin D from the sun becomes more difficult, and particularly in countries such as Germany where sunlight is limited. Thus, elderly in particular are at risk for vitamin D deficiency. Moreover, vitamin D deficiency has already been reported in AD patients. In addition, vitamin A, beta-carotene, and vitamin E deficiencies have also been reported in dementia patients. We failed to demonstrate longitudinal associations between these vitamins and AD. There is a pressing need to replicate our findings in the oldest old of other comparable longitudinal studies. To present, results of the very few RCTs or MR studies investigating vitamin D, vitamin A, beta-carotene or vitamin E with cognitive health outcomes have been contradictory, thus there is a need also replicate these studies.

Fatty acids - N-3 PUFAs are a powerful group of fatty acids important for the brain. We demonstrated that EPA was associated with all-cause dementia or AD. Effect estimates of the other fatty acids pointed towards the expected direction. Low concentrations of n-3 PUFAs might accelerate cognitive decline, therefore it is of interest for future longitudinal studies to replicate our findings, as observational studies examining the

oldest old are limited. Also, it is important to explore both absolute concentrations and proportion distributions of fatty acids, and to examine if non-linear relationships exist between the fatty acids and the outcome. Furthermore, as aforementioned RCTs should examine the whole sample, but also differentiate groups according to *APOE* ε4 status. As the role of *APOE* ε4 has shown to be important in the availability of PUFAs in the circulation and brain.

Other nutrients - In the AgeCoDe study we were not able to investigate all nutrients that might impact cognitive health. Future observational studies should consider investigating blood concentrations or dietary intake of vitamin B1, B2, B3, B5 or B7 instead of focusing on vitamin B6, folate, and vitamin B12 only. Also, blood concentrations or dietary intake of vitamin C and vitamin K need to be explored in greater detail in relation to cognitive health outcomes. Furthermore, polyphenols are strong compounds that might be of interest as well.

FOODS

Dietary intake assessment - Not all existing dietary intake assessment methods seem to be applicable to assess dietary intake in the elderly as recall bias is a general problem. Short questionnaires have been developed, but future methodological studies should further investigate if similar results can be obtained as compared to the extensive methods (Volkert and Schrader, 2013). New methods such as the assessment of dietary intake through mobile devices or web-based questionnaires are currently being developed or validated (Volkert and Schrader, 2013). The advantage is that participants only need to take pictures of the foods or meals consumed or can fill out the dietary questionnaire at their own pace. At present, it is not yet known if these “high-tech” methods are suitable for the elderly (Volkert and Schrader, 2013).

Foods - We observed that red wine and white wine intakes were associated with AD or memory decline in the elderly. Longitudinal observational studies with data on wine intake, alcohol intake, and polyphenol intake should conduct a combined analysis to further explore if the observed associations in our study are due to alcohol, polyphenols or a combination of the two. For ethical reasons, we do not recommend a wine RCT, however as described in this thesis, MR is the way forward. Additionally, for the other individual foods or food groups, we recommend to simultaneously analyze nutrients due

to nutrient interactions or between foods nutrient interactions. For example, together with fruits and vegetables it is important to explore vitamin K, vitamin E, vitamin C and carotenoids. In addition, fatty fish intake should be analyzed with n-3 PUFAs and red meat intake with SAFAs. Future RCTs can be carried out for olive oil, coffee, green tea, and fatty fish. For example, the previously mentioned PREDIMED RCT has been carried out and showed promising results for olive oil and n-3 PUFAs (Martinez-Lapiscina, et al., 2013).

Dietary patterns - An alternative for nutrient, individual food or food group analysis is dietary pattern analysis. In the introduction of this thesis, we outlined potential beneficial dietary patterns for cognitive health. Most dietary patterns include nutritional factors that counteract oxidative stress and both oxidative stress and inflammation. To date, few studies have been carried out with regard to inflammation only. For example, the *a priori* DII diet could be used to assess the level of inflammation in dietary intake. Furthermore, the Mediterranean diet has been abundantly studied in multiple populations, however, the foods listed in the Mediterranean diet are not always consumed in every population. Consequently, these populations are more likely to score low on the diet (Hodge and Bassett, 2016). For Germany in particular it might be more relevant to investigate the association between adherence to the Nordic diet and the national dietary guideline and cognitive health outcomes or to explore underlying dietary patterns through cluster analysis, PCA, or RRR.

COGNITIVE HEALTH

In nutrition epidemiology it is important to optimize nutrition as an exposure, but also to use advanced methods on the outcome side of the association. In the AgeCoDe study we made use of neuropsychological examinations to measure cognitive health and ascertain dementia diagnosis. However, ongoing and newly developed cohort studies have included amyloid - Positron Emission Tomography (PET) and CSF puncture in their study protocols (Jessen et al., 2018). These methods are able to measure biomarkers of AD such as Aß accumulation and tau (Gillette-Guyonnet et al., 2013). The DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) study is an example of a state-of-the-art clinical cohort including the aforementioned biomarkers of AD, and also has nutrition as an exposure available (Jessen, et al., 2018). For example,

a recent study investigated the association between a Mediterranean style diet and the change in biomarkers of AD using ^{11}C-Pittsburgh combound B-PET and F-fluordeoxyglucose-PET. The authors reported that lower adherence to the Mediterranean style diet was associated with more AD biomarker changes over three years of FU (Berti et al., 2018).

STUDY POPULATION

The oldest old are a fascinating group to study. Often these individuals are being asked what their secret is to reach old age. To date, not that many studies have examined the role of nutrition in this age group and also cohort studies specifically designed to investigate this group are few. An example of a centenarian study is the Georgia Centenarian Study, which included the Mini Nutritional Assessment method to assess diet (Davey et al., 2010). Thus, there is a need to examine what role nutrition can play to improve the quality of life of the oldest old, but also what we can learn from them. We encourage newly designed cohort studies to consider this particular group in their study.

4.5. CONCLUSION

The objective of this thesis was to assess the role of nutrition in relation to all-cause dementia, AD, and memory decline in the oldest old. Nutrition is a challenging exposure which can be assessed on multiple levels and with a variety of assessment methods, including dietary intake methods or the use of nutrient biomarkers. In the elderly in particular, it is important to question which assessment method is best suited to not introduce noise caused by measurement error. Short dietary questionnaires may be an answer but need to be validated and examined in multiple studies first. With our short questionnaire, we were able to replicate previous findings between red wine intake and AD, but we failed to replicate findings for the other foods and food groups, which might have been caused by measurement error. In contrast, nutritional biomarkers do not rely on memory and are less prone to bias. We observed a relationship between higher concentrations of vitamin D and EPA with AD and all-cause dementia in the oldest old. On the other hand, concentrations of vitamin E and DHA were not significantly associated with AD or all-cause dementia. It is true that epidemiological studies require a large sample size and large variability within the nutrition exposure in order to observe

an effect, particularly in nutrition analysis where small effect sizes are common. However, nutrient or food interactions also exist. For example, previous studies have observed a relationship between the subgroups of vitamin E with AD, but not with alpha-tocopherol alone. Thus, it is important to take the effect of other nutrients, foods or dietary patterns into account in the investigation. Additionally, it might also be that null findings in nutrition research are not only observed due to measurement error, but that the association is explained by other factors such as sociodemographic, lifestyle, and cardiometabolic health factors. Furthermore, the elderly included in cohort studies at a later age might be less representative of the total elderly population, who are more vulnerable and/or suffering from malnutrition. However, the GP based AgeCoDe cohort is very representative for German elderly at this age range. Additionally, we observed that the effect of nutrients (e.g. EPA) and foods (e.g. red wine) were modified by *APOE* ε4 status or by gender. Thus, it is of interest to find ways to include vulnerable elderly in studies and to explore the effects of *APOE* ε4 status and gender in greater detail. Furthermore, our significant findings were strong, but causality could not be established in our observational study designs and should be investigated further in RCTs or MR studies. At last, we were able to investigate a limited number of the wide range of existing nutrients, foods and dietary patterns. We encourage future research groups to not only replicate existing findings, but also to explore the effects of nutritional factors investigated in other medical fields. The worldwide elderly population is growing, and dementia is a multifactorial disease, therefore it is key to investigate how nutrition can contribute best to prevent, delay or reduce the progression of dementia.

5 ABSTRACT

The worldwide number of elderly is rising, and simultaneously the number of people with dementia is also increasing (Blennow, et al., 2006; Jicha and Carr, 2010). In the past 20 years the care of dementia patients has remarkably improved (Winblad, et al., 2016). Many detrimental and protective factors that affect the risk of dementia have been identified through research (Alzheimer's Association, 2016). Currently, no effective treatment of dementia exists (Winblad, et al., 2016). Thus, dementia is a challenging ongoing global public health burden on society, which needs targeted research strategies to identify treatments to delay the onset of the disease, to slow disease progression or to cure dementia (Winblad, et al., 2016). One research strategy is to investigate modifiable risk factors in relation to dementia such as nutrition, which is an important modifiable lifestyle factor. Nutrition has an impact on a wide range of diseases including cardiovascular diseases and Diabetes Mellitus (Archundia Herrera, et al., 2017), which in turn are risk factors for dementia (Alzheimer's Association, 2016). A growing body of evidence points to an important role of nutrition in the development and clinical progression of dementia (Gustafson, et al., 2015), however, many gaps still exist. Therefore, we aimed to examine the role of nutrition in relation to all-cause dementia, Alzheimer's dementia (AD) and memory decline in elderly and oldest old from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe). **Chapter 1** first introduces the reader to the concept of dementia and cognitive decline and gives an overview of known risk factors for these conditions. This is followed by a review of the current state of knowledge on the role of nutritional factors as well as their assessment methods. In **chapter 2** the general methodologies used for the presented studies are listed. **Chapter 3** contains the study results. In ***study 1*** we investigated the effects of plasma concentrations vitamin A, beta-carotene, vitamin D, vitamin E and oxidized-low density lipoprotein (ox-LDL) on clinically diagnosed AD in the oldest old over a follow-up time of seven years. We demonstrated that higher concentrations of vitamin D were associated with lower incident AD and in particular subjects with vitamin D deficiency (<20 ng/mL) were at increased risk for AD. The other vitamins and ox-LDL were unrelated to AD or all-cause dementia. Thus, our results supported the advice for monitoring vitamin D status, and to provide more sun exposure and vitamin D supplementation to subjects with vitamin D deficiency. Our null results between the other

vitamins or ox-LDL with AD or all-cause dementia were in line with previous observational studies. In ***study 2*** we aimed to assess whether the polyunsaturated fatty acids (PUFA) composition of serum phospholipids (i.e. absolute concentrations and percentage distributions), especially eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), linoleic acid (LA), dihomo-γ-linolenic acid (DGLA) or arachidonic acid (AA) were associated with increased risk of incident clinically diagnosed all-cause dementia or AD in the oldest old over a follow-up time of seven years. Our results showed that higher concentrations of EPA were associated with a lower risk of incident AD. In addition, from the literature there is a hypothesis of the influence of apolipoprotein E ε4 (*APOE* ε4) on fatty acids (Barberger-Gateau, et al., 2011; Grimm, et al., 2017.) We observed that higher concentrations of EPA were associated with a decreased risk of all-cause dementia and AD in *APOE* ε4 non-carriers, but not in *APOE* ε4 carriers. The other PUFAs were unrelated to the disease. Strikingly, aforementioned effects were only found for higher concentrations of EPA, but not for percentage distribution of concentrations of EPA and the other PUFAs, including DHA. This discrepancy might be explained by the dependency on the proportions of other fatty acids included in the fatty acid assessment or due to a lack of power for DHA. Our study supports the advice to eat fatty fish regularly. In ***study 3*** we examined whether dietary intake of red and white wine, coffee, green tea, olive oil, fresh fish, fruits and vegetables, red meat and sausages, assessed by an 8-item questionnaire, would be associated with increased risk for incident AD or memory decline over a follow-up time of 10 years. We observed that only higher red wine intake was associated with a lower risk of incident AD. Interestingly, this was true only for men, while in women higher red wine intake was associated with a higher risk of incident AD, and higher white wine intake with a more pronounced memory decline. According to our findings, women could be more susceptible to detrimental effects of alcohol. However, we also concluded that the use of a brief questionnaire is a challenge as we were only able to report an effect of red wine intake for AD, and only in men, which contradicts previous study results. **Chapter 4** contains a summary discussion of all three studies with regard to their contribution to the field. It further discusses methodological challenges of nutrition epidemiology and gives an outlook on future research perspectives.

6 LIST OF FIGURES AND TABLES

Figures

Tables

7 PUBLICATION

Study 3 (**chapter 3.3.**) has been the basis for a recent publication:

Fischer K*, Melo van Lent D*, Wolfsgruber S, Weinhold L, Kleineidam L, Bickel H, Scherer M, Eisele M, van den Bussche H, Wiese B, König HH, Weyerer S, Pentzek M, Röhr S, Maier W, Jessen F, Schmid M, Riedel-Heller SG, Wagner M. Prospective Associations between Single Foods, Alzheimer's Dementia and Memory Decline in the Elderly. Nutrients 2018;10: 1-19. * Contributed equally.

Studies 1 and 2 are currently in preparation for submission.

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9 ACKNOWLEDGEMENT

Eight years after brushing off the idea of a PhD, I am writing up my nutrition epidemiology PhD thesis in Bonn, and pursuing an academic career. Do not measure yourself with others, Prof. Oscar Franco said during our first meeting in 2014. Oscar you proved right, thank you. I could not have done this PhD by myself, a special thank you goes to:

My supervisors, **Michael,** even though you kept telling me: “I do not know nutrition”, I highly admire your endless ideas for nutrition epidemiology research. I cannot thank you enough for the fruitful discussions and always finding time in your busy schedule. Thank you for supporting me in every aspect of this PhD. I am looking forward to finish the two projects included in this thesis, but also to collaborate with you on future projects. **Frank**, thank you for being my supervisor from Cologne. I am grateful for the opportunity and trust you and Michael gave me to implement diet in the DELCODE study.

My thesis committee, **Prof. Schmid**, thank you for your time to be my Gutachter. Moreover, thank you for your support during my Joint Modelling R challenge with **Leonie**.**Prof. Klockgether** thank you for being a part of my thesis committee, I am looking forward to discussing my findings and ideas with you. **Prof. de Groot**, thank you for your time to travel to Bonn to be part of my thesis committee. It is an honor to have you as my opponent twice, as in 2012 you were my opponent during my Master thesis defense in Wageningen.

The study teams and collaborators, **AgeCoDe study team** and **participants**, thank you for setting up the study, without you this thesis would not exist. A special thank you goes to Prof. Maier, Prof. Scherer, Prof. Riedel-Heller, Prof. Bickel, Prof. van den Bussche, Prof. König, Prof. Weyerer, and Prof. Pentzek. I also thank the **DELCODE study team** and **participants** for your help and collaboration in the implementation process of nutrition in the DELCODE study. **Sarah** and **Alfredo**, thank you for the great discussions and your contributions to my manuscripts.

My colleagues, **Alex**, es war Super mit dir im Buro `*oh men´* was eine Zeit. Du schaft es auch! **Mirjam, Lisa, Luca, Steffen, Sandra** und **Ingo** vielen Dank für ihren Support, im Special am Ende. **Holger**, thanks for the great (off topic) discussions and gezelligheid!

So how many guitars do you have now?! **Johanna**, wat een toeval dat wij in DietBB onderzoek konden doen, ik mis onze dinsdag sportavond nu al. Jouw PhD gaat er zeker komen! **Prof. Turski, Nina** and **Roisin**, I cannot thank you enough for your support during my last weeks and days of my PhD. **DietBB, Prof. Heneka lab and Rhineland PhD´s and Post Docs**, it was great to be part of DietBB and the DZNE, and to have fun doing research with you. **Natascha** thank you for your support. **Roopa, Ros, Kendra** and **Sarah**, thank you ladies for your last-minute help checking my thesis for spelling mistakes.

My friends and family, **Ros, Lena** and **Ilinca** you made Bonn a home. **Elena, Alex, Enrique, Aaron, Timo, Marco, Emanuele, Alicia, Sandra** and all the others, thank you for taking my mind off my PhD during the weekends. **Mar, Hugo, kids**, **Cass**, **Anouk, Khad, Bern, Kaar, Brenda, Pety, Moira, Laris, Marlous, Gino, kids** altijd hebben jullie tijd voor mij vrijgemaakt tijdens mijn Nederland weekenden, dankjulliewel voor jullie steun uit het kikkerlandje. **Ashley**, zonder jou had ik hier niet gezeten, dankjewel dat je mij aan Ester hebt voorgesteld en dankjewel voor je support tijdens mijn PhD. **Jessica** en **Lisan**, wat lief dat jullie de moeite genomen hebben om naar Bonn te komen. Ik ben dankbaar met jullie steun en om jullie als voorbeeld te hebben. **Kim, Chantal** en **Rebecca**, wat geweldig om het master en PhD avontuur met jullie aan te gaan! **Kim**, dankjewel voor je support in de laatse dagen en uren voor het printen van de thesis en super dankjewel dat je mijn steun wilt zijn tijdens de verdediging. Lieve **pa, ma** en **Paula** dankjulliewel voor jullie steun, gebed, motivatie en zoveel meer dan ik hier op papier kan schrijven. Lieve **Vader**, U bent mijn vaste burgt waarop ik vertrouw. Dankuwel voor Uw leiding gedurende deze uitdaging. Wat de toekomst ook brenge moge, U bent mij nabij.