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## Nutrition and metabolic profiles in Alzheimer's disease

de Leeuw, F.A.

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# **Chapter 1**

**General introduction and thesis outline**

## General introduction and thesis outline

Dementia is a major global health problem and the number of people living with dementia is rapidly rising as a result of the worldwide ageing population. In February 2020, Alzheimer Europe announced that the prevalence of dementia is expected to double between 2018 and 2050, resulting in an estimated 19 million people living with dementia in Europe [1].

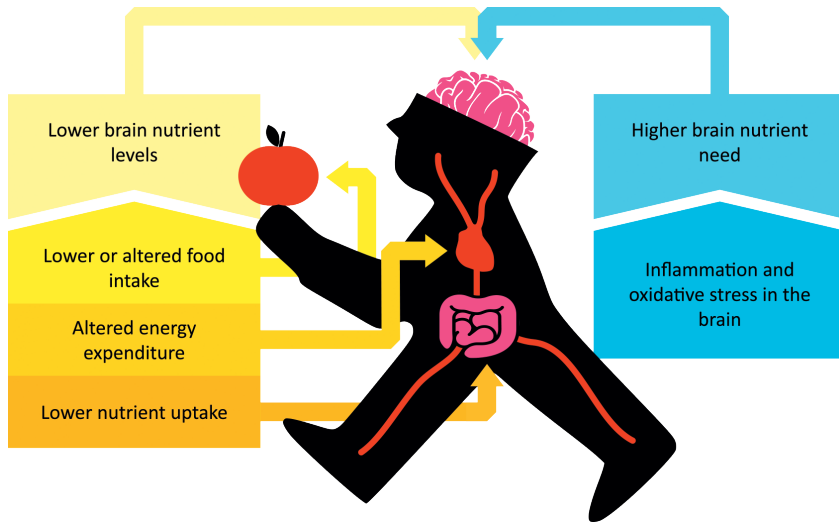
Alzheimer's disease (AD) is the leading cause of dementia, accounting for approximately two thirds of all dementia cases [2]. The disease process of AD starts years before the onset of dementia [3, 4]. Dementia is preceded by a clinical stage with cognitive deficits, that are not sufficient for a dementia diagnosis; mild cognitive impairment (MCI) [5]. In an even earlier stage, some individuals visit the memory-clinic with subtle cognitive complaints that cannot be objectified in cognitive tests. These cognitively normal individuals are referred to as people with subjective cognitive decline (SCD) [6]. Individuals with SCD and MCI are at increased risk for dementia [7, 8]. Therefore, these patients provide us with a unique opportunity to study the disease trajectory of AD.

Neuropathological hallmarks of AD are the accumulation of amyloid- $\beta$  plaques and neurofibrillary tangles [9]. Other factors such as vascular damage, inflammation and oxidative stress are important contributors to the neurodegenerative process of AD [10-12]. Together these pathological changes are thought to result in synaptic dysfunction, synaptic and neuronal loss and brain atrophy [3].

Nutrients in the brain are essential for normal physiological functioning and to protect neurons against oxidative stress and cell damage [13]. Accumulating evidence suggests that diet and nutritional status also play an important role in AD [14]. Changes in nutritional status are already reported in early stages of AD and are associated with faster cognitive decline, but the exact role of nutrition in predementia stages remains largely unknown [15-17].

## Nutrition and Alzheimer's disease

Nutritional status in AD might be compromised for a number of reasons (**Figure 1**). Firstly, worsening of taste and smell has been reported in AD and might lead to changes in food preferences and reduced food intake [18, 19]. Secondly, AD-related changes in metabolism, including changes in energy expenditure or gut microbiota, might lower nutrient uptake or increase nutrient requirements [20-22]. Lastly, higher levels of oxidative stress and inflammation associated with AD, could raise the need for specific nutrients [20, 23].



**Figure 1** Possible pathways for nutritional change in AD (Illustration by Daan Janssen).

Multiple nutrients have been associated with both risk of AD-type dementia and rate of cognitive decline [24-26]. The study of dietary patterns might help to capture the combined and synergistic effects of multiple nutrients. For example, the Mediterranean diet has been associated with a lower risk of AD and age-related cognitive decline [27, 28]. A Mediterranean diet consists of high intake of vegetables, legumes, fruits, cereals and fish and low intake of saturated fatty acids, meat, poultry and dairy products [29]. The exact mechanisms by which the Mediterranean diet exerts its beneficial effects is not known, but possible pathways have been suggested. In comparison to the typical Western diet, the Mediterranean is high in vegetable fat from nuts and olive oil and low in animal fat from dairy and meat. This reduces levels of low-density lipoprotein (LDL) cholesterol and consequently lowers the risk of cardiovascular disease [29, 30]. Cardiovascular risk factors such as hypertension and hypercholesterolemia at mid-life have been associated with an increased risk of dementia [31, 32]. In addition, the Mediterranean diet is very rich in antioxidant and anti-inflammatory nutrients such as vitamins, minerals and omega-3 fatty acids. Oxidative stress and inflammatory damage are important characteristics of AD pathology [33]. Nutrients such as omega-3 fatty acids and vitamin E have been demonstrated to exert anti-oxidative and anti-inflammatory effects in brain animal models [34, 35]. Moreover, a higher intake of anti-oxidant and anti-inflammatory nutrients has been associated with a lower risk of AD in population-based studies [24, 36]. Finally, the Mediterranean diet contains a lower protein intake in comparison to the typical Western diet [29]. Higher intake of proteins, in particular branched chain amino acids, have been associated with obesity and type 2 diabetes [37, 38]. Remarkably, meta-analyses of multiple independent cohorts showed that lower

blood levels of the branched chain amino acids valine, leucine and isoleucine were associated with an increased risk of (AD) dementia and cognitive decline [39, 40]. These conflicting findings on the relation between branched chain amino acids and cardiovascular and cognitive health remain to be elucidated. Overall, a number of biological mechanisms have been suggested to explain the relation between nutrition and AD. A deeper understanding of the nutritional determinants and mechanisms in humans is, however, lacking.

## **Determinants of nutritional status**

Factors that contribute to change in nutritional status can be investigated by looking at levels of nutritional biomarkers or metabolites in biofluids. Markers in blood are most commonly studied, as they are relatively noninvasive and easy to obtain. A nutritional biomarker can be defined as any biological indicator of nutritional status corresponding to intake or metabolism of dietary components [41]. Metabolites refer to a wider concept of all small molecules that are involved in metabolism [42]. Metabolites are mostly measured using platforms that apply nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry (MS) to allow rapid quantification of many metabolites with minimal sample preparation and at low costs [43]. Metabolites in blood, including amino acids, lipoproteins and fatty acids, have been associated with cognitive function and risk of AD [39, 44]. While meta-analyses of large, well-defined cohorts have improved replication of findings, most studies were of population-based cohorts and metabolic change in the symptomatic phase of AD remains largely undefined.

A methodological limitation of (untargeted) metabolomics studies is the varying list of measured compounds across studies which hamper the comparison of results. Moreover, these large datasets can cause multiple testing and collinearity problems. Studies of metabolic patterns or networks might reduce this problem and have the advantage of getting a more integrated view on metabolic functionality. This can be useful to identify the affected metabolic pathways and to understand the development of metabolic change in AD.

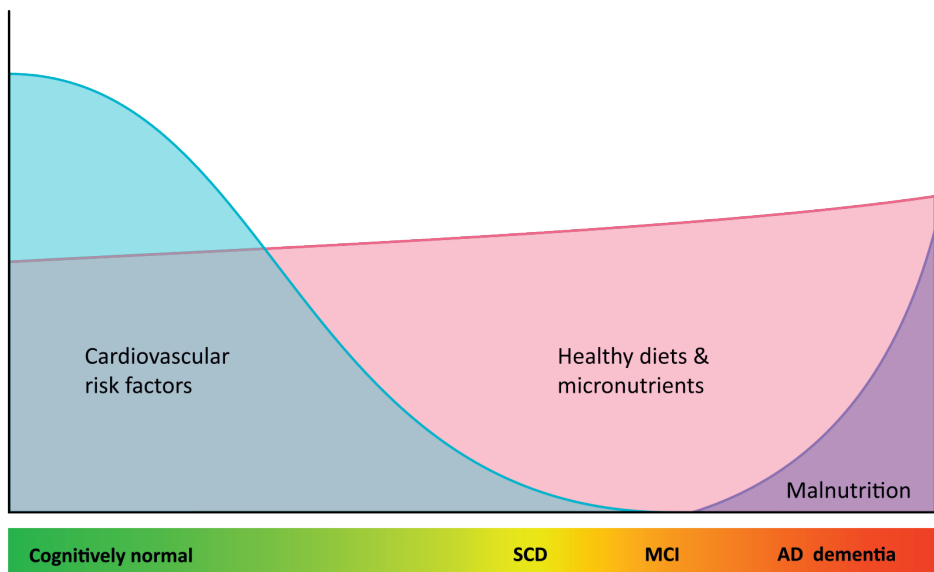
## **Biological mechanisms between nutritional status and neuronal damage**

Animal models have facilitated formulation of biological hypotheses on the mechanistic pathways underlying the relation between nutrition and AD. Validation of these hypotheses in humans is complicated for a number of reasons. Firstly, food intake does not perfectly correlate with brain nutrient status, as many genetic and metabolic factors influence the availability of nutrients to brain tissue [45, 46]. While highly controlled diets with supraphysiological doses

of specific nutrients are feasible in animal studies, this is far more complex in humans. Secondly, examination of post-mortem brain tissue remains one of the most important approaches to identify determinants of AD. Large community-based pathologic cohorts that provide a relatively unbiased sample of the general population are, however, scarce. Lastly, biological criteria for AD that can be measured in vivo are relatively novel and measurement methods are still evolving. Future nutrition studies will be able to test biological hypotheses by including cerebrospinal fluid (CSF) or positron emission tomography (PET) measures of amyloid positivity or imaging markers characteristic of AD [47-49]. More insight into the biological pathways between nutrition and AD might help us understand the mixed findings from epidemiological studies and differentiate causal nutritional factors from those that are merely a consequence of the disease process.

## The association between nutritional biomarkers and clinical progression in AD

Longitudinal studies on nutritional factors enable us to build theoretical models on the influence of these factors at specific time windows.



**Figure 2** Conceptual model of the influence of nutritional factors across the disease course (Illustration by Daan Janssen).

As illustrated in **Figure 2**, epidemiologic studies have identified mid-life cardiovascular disease as an important risk factor for dementia [31, 32].

Interestingly, associations between cardiovascular risk factors and dementia are less clear in late-life and in symptomatic stages of AD [31, 50-52]. It has been hypothesized that these tempered associations are a consequence of involuntary weight loss, malnutrition and lower overall health [53, 54]. The exact role of cardiovascular disease in early AD, however, needs to be further investigated. Healthy diets, such as the Mediterranean diet, and higher intake of specific micronutrients might be associated with risk of dementia and clinical progression throughout the disease course [55, 56]. In addition, malnutrition becomes more prevalent in symptomatic stages of disease and is associated with faster cognitive decline [15, 17, 57]. For cholesterol levels, a trajectory similar to that of cardiovascular risk factors has been suggested; i.e. high cholesterol levels are a risk factor at midlife, while this is less clear in clinical stages of AD [50, 51]. Trajectories for most nutritional biomarkers are, however, unknown. Longitudinal studies that examine nutritional biomarkers across the cognitive spectrum of AD are therefore needed.

## **Nutrition research in memory-clinic and clinical-pathologic cohorts**

### **NUDAD project**

A considerable part of this thesis was executed in the context of the ‘Nutrition, the unrecognized determinant of Alzheimer’s disease’ (NUDAD) project. Current knowledge of the role of nutrition in AD is largely based on community-dwelling and institutionalized individuals. To understand the role of nutrition in memory-clinic patients, the NUDAD project was initiated in 2015. NUDAD is a prospective cohort study, nested within the Amsterdam Dementia Cohort, that aims to identify nutritional determinants in 552 memory-clinic patients with SCD, MCI and AD-type dementia [15]. All patients underwent standardized cognitive screening, including neuropsychological and neurological examination, imaging of the brain, blood sampling and a lumbar puncture. In addition, we measured body composition, nutritional biomarkers, nutritional status and food intake using detailed questionnaires. A subgroup of 92 NUDAD participants additionally participated in an in-depth study on nutrition, including smell, taste, food preferences and energy expenditure [19]. The NUDAD project has a follow-up of three years which allows us to also evaluate associations of nutritional factors with clinical progression. Follow-up took place by routine annual visits to our tertiary memory-clinic in which neuropsychological and medical examination was repeated. If participants were unable or did not want to attend clinical follow-up, telephone interviews were held in which change of diagnosis, living situation and self-reported change in cognitive function were discussed. In addition to the prospective NUDAD cohort, a retrospective cohort of 299 memory-clinic patients with SCD and MCI was assembled to identify

promising nutritional biomarkers associated with clinical progression, which could then be validated in the prospective NUDAD cohort.

## The Rush Memory and Aging project

The second chapter of this thesis was executed in the context of the Rush Memory and Aging Project (MAP). The MAP study is a clinical-pathologic cohort study of 2200 community residents of the Chicago area [58]. The main goal of MAP is to identify risk factors for cognitive decline and incident AD-type dementia. Started in 1997, it is unique for its long inclusion and follow-up period. At enrollment, MAP participants are free of dementia, agree to undergo annual clinical and neurological evaluation, and a brain autopsy at death. Annual dietary assessment of MAP participants started in 2004. Additionally, brain nutrient levels have been measured in subgroups of deceased participants.

## Aim of this thesis

The main goal of this thesis was to identify nutritional and metabolic determinants of AD in the brain, CSF and blood. To this end, we aimed to investigate:

- Pathways between nutrient status and neuronal damage in post-mortem brain tissue;
- Blood-based metabolic dysregulation across the cognitive spectrum of AD;
- Associations of blood and CSF nutritional biomarkers with clinical progression in a memory-clinic setting.

## Thesis outline

To address the first aim, **chapter 2** focuses on the underlying mechanisms of the relation between vitamin E and AD dementia in a sample of 113 deceased and autopsied participants of the Rush MAP community cohort. In **chapter 2.1** we first assess the association between brain vitamin E (tocopherol) levels and microglia density, and subsequently in **chapter 2.2** of brain tocopherol levels with presynaptic protein levels in post-mortem brain tissue. **Chapter 3** addresses the second aim, by examining AD-related metabolic change. In **chapter 3.1**, we compare blood-based metabolites between patients with AD-type dementia and controls, and describe metabolic changes both as individual metabolite shifts as well as from a network perspective. To understand if blood-based metabolites concentrations reflect AD-related brain changes, we study how blood-based metabolites relate to imaging markers of AD in three independent cohorts in **chapter 3.2**. In **chapter 4**, we study nutritional biomarkers as determinants of clinical progression in a memory-clinic setting. To identify nutritional factors that lead to nutritional biomarker insufficiencies,



reliable estimates of nutrient intake are needed. Therefore, in **chapter 4.1**, we investigate the relation of nutrient intake as assessed by a food frequency questionnaire and nutrient status, measured by blood nutritional biomarkers in a memory-clinic cohort of controls, MCI and AD-type dementia patients. **Chapter 4.2** identifies individual nutritional biomarkers and profiles in blood and CSF that were associated with clinical progression in a retrospective memory clinic cohort of patients with SCD and MCI. In **chapter 4.3**, we extend and validate our findings on nutritional biomarkers and clinical progression in a prospective cohort of SCD, MCI and AD-type dementia.

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