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Nutritional Status, Cognitive Performance, and Vascular Function with Advancing Age: Complexity in Medicine

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Die dieser Arbeit zugrunde liegende interventionelle klinische Studie, die europaweit über drei verschiedene Länder stattgefunden hat, wurde durch die NeuroExercise Group durchgeführt, wobei die Testung deutscher Probanden an der Deutschen Sporthochschule in Köln, Deutschland unternommen wurde.

Die Anleitung zur von mir selbst durchgeführten statistischen Auswertung der Daten erfolgte durch Dr. Tim Stuckenschneider, Geriatric Medicine, Department for Health Services Research, School of Medicine and Health Sciences, Carl von Ossietzky Universität, Oldenburg, Deutschland. Die dieser Arbeit zugrundeliegende Publikation „Influence of a 12-month structured exercise program on the micronutrient-cognitive fitness-physical association

profiles in mild cognitive impairment“ in der Zeitschrift *Journal of Alzheimer’s Disease Reports* (Impact-Faktor 4.160) wurde eigenständig von mir verfasst. Eine genaue Darstellung des Eigenanteils kann meiner schriftlichen Erklärung über den von der Doktorandin geleisteten Beitrag zu der Arbeit eingesehen werden, welche von allen Coautoren unterschrieben wurde.

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Das Lektorat *Mentorium* hat die Endfassung dieser Arbeit grammatikalisch und sprachlich überarbeitet, hat jedoch weder einen Anteil an der geistigen noch an der inhaltlichen Gestaltung dieser Arbeit.

Falls ich mich im Rahmen dieser Arbeit auf Ergebnisse anderer Arbeiten beziehe, habe ich dies kenntlich gemacht.

Erklärung zur guten wissenschaftlichen Praxis:

Ich erkläre hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zu Umgang mit wissenschaftlichem Fehlverhalten (Amtliche Mitteilung der Universität zu Köln AM 132/2020) der Universität zu Köln gelesen habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen.

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Ich habe euch so lieb.

Contents

Abbreviations

AD: Alzheimer's disease

SCI: Subjective Cognitive Impairment

MCI: Mild Cognitive Impairment

AE: Aerobic Exercise Group

S&T: Stretching & Toning Group

CG: Control Group

DNA: Deoxyribonucleic acid

Aß protein: Beta-amyloid protein

SCD: Subjective cognitive decline

SD: Standard deviation

CSF: Cerebrospinal fluid

FDG-PET: [18F]-fluorodeoxyglucose positron emission tomography

PET: Positron Emission Tomography

pTau: Phosphorylated tau

ttau: Total-tau protein

MRI: Magnetic Resonance Imaging

NFL: Neurofilament light

NMDA: N-Methyl-D-Aspartate

GWAS: Genome-wide association studies

APOE: Apolipoprotein E

IFN-γ: Interferon Gamma

IL-1β: Interleukin-1ß

TNF-α: Tumor Necrosis Factor Alfa

CNS: Central Nervous System

CRP: C-reactive protein

T2DM: Type II Diabetes Mellitus

OS: Oxidative Stress

DHA: Docosahexaenoic Acid

MeDi: Mediterranean Diet

DASH: Dietary Approach to Stop Hypertension

MIND: Mediterranean-DASH Diet Intervention for Neurodegenerative Delay

ROS: Reactive Oxygen Species

PUFAs: Polyunsaturated Fatty Acids

SFAs: Saturated Fatty Acids

MUFAs: Monosaturated Fatty Acids

ALA: Alpha-Linolenic Acid

LA: Linolenic Acid

AA: Arachidonic Acid

EPA: Eicosapentaenoic Acid

DHA: Docosahexaenoic Acid

COX-2: Cyclooxygenase 2

NF-kB: Nuclear Factor 'kappa-light-chain-enhancer' of Activated B-cells

BBB: Blood-Brain Barrier

MMSE: Mini-Mental State Examination

BCO1: ß-carotene-15, 15'-oxygenase

BCO2: β-carotene-oxygenase 2

VDR: Vitamin D Receptor

CR: Cognitive Reserve

CBF: Cerebral Blood Flow

CAA: Cerebral Amyloid Angiopathy

NVU: Neurovascular Unit

VSMC: Vascular Smooth Muscle Cells

SPECT: Single Photon Excitation Computed Tomography

RAGE: Receptor for Advanced Glycation Endproducts

LRP: Low-density Lipoprotein Receptor Related Protein-1

ISF: Brain Interstitial Fluid

VEGF: Vascular Endothelial Growth Factor

BDNF: Brain-Derived Neurotrophic Factor

LDL: Low-Density Lipoprotein

HDL: High-Density Lipoprotein

RAS: Rat Sarcoma Virus

FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

CGA: Comprehensive Geriatric Assessment

CBB: CogState Brief Battery

TMT A/B: Trail Making Test A/B

HRV: Heart rate variability

PAT: Peripheral arterial tone

Selfy-MPI: Selfy – Multidimensional Prognostic Index

HPLC: High Performance Liquid Chromatography

DET: CogState Detection Task

IDN: CogState Identification Task

OCL: CogState One-Card Learning Task

ONB: CogState One Back Task

1. Deutsche Zusammenfassung

Jeder wird früher oder später mit der Tatsache konfrontiert, dass wir altern. Diese Realisierung kann in verschiedenen Teilaspekten des Alltags auftreten und kann damit früher oder später im Leben ein Thema werden. Je älter man wird, desto mehr kommen Gedanken und Sorgen über die Vergesslichkeit auf. Dies ist insbesondere ein Thema der zunehmend alternden Gesellschaft. Einerseits gibt es einen Zuwachs an Senioren, die kognitiv fit und selbstständig sind, andererseits auch einen erheblichen Anteil an Senioren, die wegen multiplen chronischen Erkrankungen das alltägliche Leben nicht mehr selbstständig bewältigen können. Daraus ergibt sich die Frage, welche Faktoren dazu beitragen, dass manche Menschen bis ins hohe Alter ihre kognitiven Fähigkeiten gut erhalten können und wie wir diese Erkenntnisse therapeutisch anwenden können. Vorerst ist es wichtig aufzuzeigen, dass nicht jede kognitive Alterung gleich Demenz oder die allbekannte Alzheimer's Disease (AD) darstellt, sondern es verschiedene Vorstufen der kognitiven Einschränkung gibt. Dazu gehören zum einen die subjektive kognitive Einschränkung, im Englischen *subjective cognitive impairment (SCI)* und die milde kognitive Einschränkung, *mild cognitive impairment (MCI)*. Im Hinblick auf den wachsenden Anteil der älteren Bevölkerung ist es wünschenswert diese Vorstufen schon früh zu erkennen, um zeitnah mit einer Therapie beginnen zu können. Die erstmalige Entwicklung eines wirksamen multimodalen Therapiekonzeptes erfordert jedoch im ersten Schritt, dass dieses komplexe Geschehen und alle Parameter, die einen Einfluss darauf nehmen, genauer erforscht und verstanden werden. Hierzu wurden bereits verschiedene Studien durch die Forschungsgruppe der Altersmedizin an der Uniklinik Köln durchgeführt. Ein großer Baustein davon stellte auch die NeuroExercise Studie unter der Leitung der Deutschen Sporthochschule Köln dar, die in drei europäischen Ländern (Irland, Niederlanden und Deutschland), durchgeführt wurde. Hierbei wurde eine Randomisierung der 181 Probanden mit MCI in drei Gruppen vorgenommen, die *Aerobic Exercise Gruppe (AE; n=60)*, die *Stretching and Toning Gruppe (S&T; n=65*) und die *Kontrollgruppe (CG; n=58).* Ausgenommen von der CG unterzogen sich die anderen beiden Gruppen einer 12-monatigen Intervention, die wöchentlich dreimal 45 Minuten durchgeführt wurde. In der Veröffentlichung, die dieser Arbeit zugrunde liegt, wurden ausschließlich die Probanden aus Deutschland begutachtet. Nach einem Jahr der sportlichen Intervention wurden verschiedene antioxidative Mikronährstoffe im Zusammenhang mit kognitiver sowie physischer Leistung bei den Probanden, die zum Zeitpunkt der Baseline und dem Follow-up Blut abgegeben hatten, analysiert. Hierbei stellten sich mehrere signifikante Korrelationen zwischen bestimmten Mikronährstoffe vor der Intervention des körperlichen Trainings mit kognitiven Outcomes dar, sowie mit Physischen nach der Trainingsintervention. Die Interaktionen, die durch diese Studie beobachtet werden konnten, regen dazu an, intensiver in das Feld der Effekte eines multimodalen Ansatzes, den

Lebensstil der Menschen betreffend, einzutauchen. Hiermit abzielend auf den Lebensstil mit Inklusion der Ernährung, Aktivität, Schlafhygiene, jedoch auch geistiger Fitness, der Funktionalität des sozialen Umfeldes, als auch medikamentösen Ansätzen und noch vielen weiteren Aspekten.

2. Summary

Demographic changes and the growing age gap underline the importance of preventive lifestyle strategies, which have shown promise in slowing down or preventing age-related cognitive decline. However, evidence on the reciprocal longitudinal relationships between nutrition biomarkers and cognitive and physical performance are lacking. Studying nutritional, cognitive and physical profiles over time may help to overcome this knowledge gap. The relationship of plasma levels of the robust nutritional- and antioxidant defense-related biomarkers carotenoids and tocopherols with both indicators of cognitive and physical performance in persons with MCI participating in a structured exercise program was investigated by analyzing data from 40 MCI participants of the JPND Neuroexercise study. Participants underwent a blood withdrawal for the analysis of plasma concentrations of six carotenoids, two tocopherols and retinol prior to and after one year of structured exercise. All participants underwent a broad spectrum of cognitive and physical performance tests. Significant associations between lipophilic micronutrients and cognitive/physical measures were observed, that were previously found to play a role in cognitive and physical frailty. In particular, lutein, zeaxanthin and lycopene were confirmed as robust, reliable, stable indicators of nutritional defense. Interestingly, in relationship to cognitive and motoric functions, the micronutrients measured in most of the study participants were shown to associate with cognitive measures prior to the physical training program and with indicators of motoric function after a physical exercise program [1]. The observed interaction between physical, nutritional, and cognitive measures warrants future investigation into the effects of multidimensional lifestyle interventions to prevent cognitive and physical impairment.

3. Introduction

3.1. The Process of Aging

The process of aging has captured the fascination of humans for centuries. Looking back to early antiquity until now, the same issues are still to be explained. Especially from a scientific point of view, many questions remain unanswered.

One recurrent question is whether the human organism developed as the result of a chain of coincidentally occurring events or a systematic, regulated process indicating potential to adapt to environmental influences. Aging is connected to an increasing loss of physiological integrity, leading to a reduced function and an elevated vulnerability to death [2]. Research has shown that the rate of aging is at least partially influenced by biochemical processes and genetic pathways. The process itself has been described by several hallmarks in the classical way, from telomere curtailment and genomic damage to mitochondrial dysfunction and stem cell pool collapse, among many others [2].

In 2013, the first edition of *hallmarks of aging* was published, suggesting nine systemic, cellular and molecular hallmarks of aging, including “DNA [deoxyribonucleic acid] instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication” [2]. Subsequent research attempted to challenge these findings, but the resistance that of these hallmarks towards the scrutiny of thousands of researchers over the years has shown their importance. In 2023, ten years after the first edition, Lopez-Otin et al. published a subsequent edition, updating their findings on the *hallmarks of aging* [3]. A statistically higher chance of shared genomic characteristics and co-occurrence concerning human age-related diseases exists when being interconnected to the same hallmark then to different ones. Through their interaction and dependence, a general distinction among the hallmarks proves to be diffuse and a classification therefore random. The following three criteria were suggested as an obligatory application for each hallmark of aging: “(1) the time-dependent manifestation of alterations accompanying the aging process, (2) the possibility to accelerate aging by experimentally accentuating the hallmark, and - most decisively - (3) the opportunity to decelerate, halt, or reverse aging by therapeutic interventions on the hallmark” [3]. The aforementioned twelve hallmarks of aging were suggested after including all the latest research findings: “genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication,

chronic inflammation, and dysbiosis" [3]. Their interdependence and effects among themselves accentuate the complex process of aging and its entity to be perceived as a whole. Consequently, future research should contemplate each hallmark as an entry point [3].

Cellular senescence is one component of the aforementioned hallmarks and is believed to play a pivotal role in the aging of organisms. It assumes that cultured cells lose their capacity to proliferate irreversibly as a response to stress [4]. This has been conceptualized for replicative diploid human cells, although it must be considered that the majority of human cells are non-proliferating [5,6]. Another recently discovered aspect is a senescence-like mechanism, which is proliferation-independent in post-mitotic cells [7,8]. These post-mitotic cells include neurons, which may indicate that senescence mechanisms could play an important role in neurodegenerative disorders [9]. This neuronal concept is termed amitosenescence and implies that senescence and aging are interdependent in their functionality [10,11].

However, before diving into this matter further, it should be stated that there are different meanings to the terms of "cell aging" and "cell senescence", even though they are sometimes used as equivalent [12]. It is still controversial whether aging is a disease or just a state of disease or neither [13].

Scientist have attempted to explain and build theories around the process of aging for many decades. For a simplified presentation of these attempts, a rough classification can be applied, with the main categories being program theories, damage theories and the combined theories [14]. The following is a brief collection of some theories, with number four as the main focus in this work:

1. The programmed theory: Aging is a genetic program built to benefit the following generations which results in aging and death [15].
2. The evolutionary theory: Aging is caused by an accumulation of mutations, which display positive or no effects in the early stages but can lead to harmful effects later on if not removed through natural selection [16,17].
3. The hyperfunction theory: Aging comes about due to a hyperactivity of genes during the reproductive timeframe leading to aging through cellular hypertrophy [18].
4. The free radical theory: Aging involves the antioxidant-system getting overwhelmed by a consecutive build-up of oxygen species, which presumably leads to damage of various components of the cell. [19]

An overview of still unresolved matters is shown in the figure below, where green shows the scientifically accepted points and red shows still unresolved aspects.

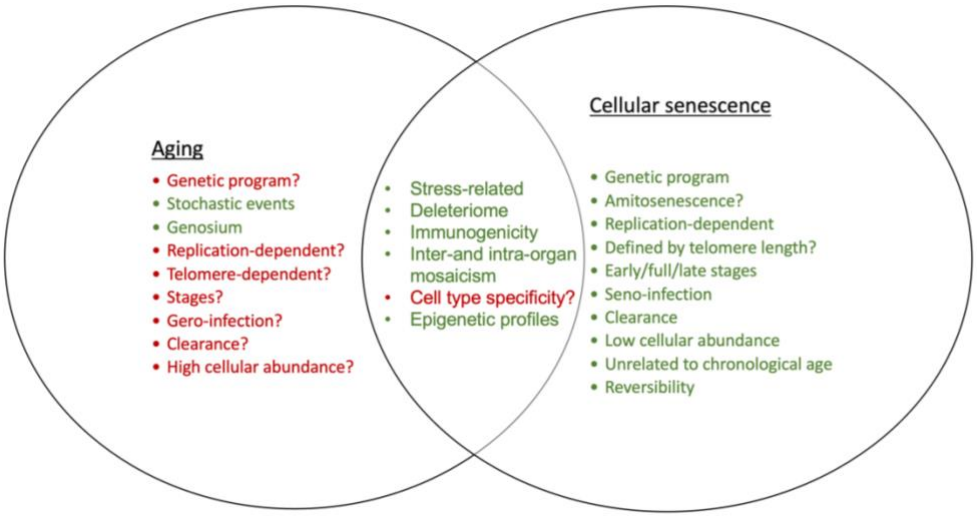

Figure 1. Aging and cellular senescence – overlapping scientific matters

3.2. Dementia and Nutrition

As a demographic shift occurs and life expectancy is rising, the number of aging-associated diseases increases substantially [20]. Among those, dementia in particular can be described as a syndrome rather than a disease. Any disorder showing interference with the domestic, occupational or social functioning from one's previous level of cognition can be assigned to the group of dementia. Primary neuropsychiatric, neurologic, and medical conditions are counted to the myriad causes of dementia [21]. For the initial evaluation and diagnosis of dementia, the following four elements should be included: "l) thorough clinical history; 2) neurological examination, with an emphasis on the assessment of mental status; 3) selective labs to screen for selected metabolic/physiologic abnormalities (e.g., basic chemistries, thyroid panel, B12, Vitamin D); and 4) a structural brain scan, with magnetic resonance imaging (MRI) preferable to computed tomography whenever possible" [21]. Dementia syndromes can be divided into two broad categories of disease: neurodegenerative and non-neurodegenerative. A more detailed categorization is shown in the figure below [21].

Neurodegenerative	Non-neurodegenerative
Alzheimer disease	Vascular dementia (multi-infarct dementia, small-vessel ischemic disease, chronic/subacute subdural hematomas, hypoxic/ischemic encephalopathy)
Dementia with Lewy bodies, Parkinson disease dementia	Normal pressure hydrocephalus
Frontotemporal lobar degeneration	Metabolic causes (hypothyroidism, chronic uremia, malnutrition, Cushing syndrome)
Multiple system atrophy	Autoimmune causes (limbic encephalitis, Hashimoto encephalopathy, voltage-gated potassium channel encephalopathy)
Non-Parkinsonian movement disorders (Huntington disease, Wilson disease, Dentatorubral-pallidoluysian atrophy)	Depression, bipolar disorder (historically called "pseudo-dementia")
Alcoholic cognitive impairment/dementia	Neoplastic/paraneoplastic causes (NMDA-receptor and CRMP-5-antibody encephalopathy, brain tumor)
Chronic traumatic encephalopathy	Infectious causes (syphilis, HIV-associated neurocognitive disorder)
Prion disease (Creutzfeldt-Jakob disease, fatal familial insomnia)	Toxic causes (lead, arsenic, organophosphate pesticides)
Dementia related to multiple sclerosis	Vasculitides (primary vasculitis of the central nervous system, Behçet disease, SLE-related)
Motor neuron disease (Amyotrophic lateral sclerosis, Primary lateral sclerosis)	Vitamin deficiency (B12, thiamine, niacin, folic acid)

CRMP = collapsin response-mediator protein; HIV = human immunodeficiency virus; NMDA = *N*-methyl-D-aspartate; SLE = systemic lupus erythmatosus.

Figure 2. Examples of Selected Cognitive Impairment/Dementia Syndromes, Divided into Two Broad Categories: Neurodegenerative and Non-neurodegenerative

AD, a sub-form of dementia, is the common cause of dementia in Europe and North America and therefore the focus of the present work [20]. The disease may start to develop decades before any cognitive symptoms manifest, which is described as the preclinical AD [22,23].

The simplified distinctive features of AD include a buildup of misfolded tau proteins in the form of neurofibrillary tangles of tau protein in the neurons, an aggregation of beta-amyloid (Aß) protein into extracellular senile plaques, as well as neuronal and synaptic loss [24-26]. Aß

pathology propagates across allo- and neocortical regions of the brain in the beginning and downstream expansion, only spreading to the brainstem in late stages of the disease [27], while tau pathology first appears in the entorhinal cortex and the locus coeruleus with a following up-stream expansion to the limbic and isocortical regions [28].

With dementia currently being incurable, it causes significant concerns for public health [29]. The pathophysiology of AD has various aspects and only gets diagnosed in a late state of the disease in the majority of the cases [29]. The causes of AD may be said to be multifactorial as it might be triggered by complex interactions, midst genetic, epigenetic and environmental factors [30]. With progressing age, multifactoriality increases, which is the main risk factor for cognitive impairment. The vast majority of dementia patients are age 65 or older [31]. Considering this aspect more research has to be done in the field of early AD diagnosis to slow the progression down [29].

Symptoms of AD that might be visible before a clinical diagnosis is obtained may include anxiety, mood swings and disturbance of sleep. Additionally, more unspecific symptoms, such as aggressive behavior, delusion or confusion, can arise [32]. AD commonly occurs through progressive cognitive dysfunction, as behavioral or speech and memory disorder [33,34].

The next stage is described as subjective cognitive decline (SCD), in which individuals' self-perception includes a subjective, persistent decrease in cognitive function, which is neither correlated to an acute event nor shows evidence of objective cognitive impairment influencing daily functioning and cognitive performance assessed through neuropsychological testing used to detect MCI, adjusted for age, sex, and education. Nonetheless, this subjective decline in cognitive function is garnering an increased clinical interest as the number of this particular group seeking medical advice is rising, while the evidence shows an association with an increased risk of developing an objective cognitive decline [35-38]. In this sense, *decline* describes the deterioration of cognitive capacities experienced subjectively. The term *impairment*, as in SCI, is also used often in research. However, the temporal course of subjective cognitive change is not entirely covered by the term *impairment* as it can also describe a state of a stable and chronic nature. Further, SCI might suggest a certain severity level concerning SCD, being depicted by a subjectively experienced impairment, rather than just the deterioration of cognitive function compared to a prior point in time [29,36,39,40]. A coding system is proposed in SCD studies, ciphering the severity of impairment experienced because of a decrease in cognitive capacity and allowing the assessment of the specific prediction of AD based on SCI within the SCD frame [36].

The following stage is characterized by MCI, preserving the individual's daily functioning as well as their independence and characteristically presenting with an objective cognitive impairment [41]. In individuals with SCD, a decline to dementia in the future was found to be at 14% and a decline to MCI in 27% of individuals [35]. Comprehensive neuropsychological test batteries are recommended to assess multiple cognitive domains with sex-adjusted, age-adjusted and education-adjusted data [42]. So far, no single cutoff has been universally accepted to distinguish cognitive impairment between that occurring in SCD and that occurring in MCI. Standard deviation (SD)-based cutoffs are a suggested approach with, for example, "scores of >1.5 SD below the normative mean on any test within a specific cognitive domain; scores of >1.0 SD below the normative mean on at least two separate tests of one cognitive domain; or a score of >1.0 SD below the normative mean in at least three cognitive domains" [43]. A higher score than the cutoffs is expected in individuals with SCD, while individuals with MCI and dementia would be expected to score below the cutoffs. Furthermore, the extent of cognitive impairment can be determined alternatively through a clinical decision based on the collected available neuropsychological and clinical information [38,44,45].

Biomarkers in the cerebrospinal fluid (CSF) and imaging has reached a critical importance in detecting disorders leading to behavioral and/or cognitive impairment [46-49]. [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) enables the detection of suggestive patterns of hypometabolism which are associated with early neuronal and synaptic dysfunction [50]. A rise in retention of amyloid Positron Emission Tomography (PET) tracer and a decrease in Aβ42 or Aβ42/Aβ40 ratio in the CSF indicate a pathological deposition in the brain tissue [51]. Tauopathy is denoted through a rise in CSF phosphorylated tau (pTau) and tau-PET tracers' accumulation with total-tau protein (ttau) being especially associated with AD [52-54]. Magnetic Resonance Imaging (MRI) tools are used to detect cerebrovascular damage and to assess the extent of regional atrophy [53]. Biomarkers of tau aggregation and amyloid deposition are assumed to possess the ability to detect the disease in patients in the early stages, as research suggests the beginning of pathological processes starts more than two decades before symptoms become apparent [55].

As CSF biomarkers and the use of amyloid-PET are a rather costly and/or invasive method, plasma biomarkers are more promising regarding the creation of procedures with reduced risk and improved accessibility in the future [56-59]. As detecting the early stages before the diagnosis of AD is a critical step in terms of future therapies, accessible tests for pre-dementia stage identification are increasingly important [60,61].

Another unspecific biomarker for neurodegeneration that should be considered is the neurofilament light (NFL), which is measurable in the CSF and the plasma [62]. An association between MRI characteristics, which show in early AD stages and throughout the disease progression, as well as cognitive deficits with the NFL can be found. Amyloid deposition in amyloid-PET were associated with changes in plasma NFL concentration and an association with poorer longitudinal cognition was shown in higher baseline plasma levels [63-65].

Previous research has established various risk factors, such as insulin resistance, obesity and hypertension, which put the individual at greater risk to entering the first stages of the development of AD and are modifiable using environmental and lifestyle changes as the first pillar [22,23]. Thus far, there is no cure or effective treatment for AD. Only symptomatic treatment can be used to slow down its progression [66].

In 2005, the first line of treatment as the second pillar consisted of molecular prevention like Acetylcholinesterase inhibitors, which slow the process of acetylcholine breakdown, as well as N-methyl-D-aspartate (NMDA) receptor antagonists through blocking the glutamate receptors, which are drugs currently used in the therapy of AD [67]. Another promising treatment approach for AD is immunotherapy against Aß. Diverse species of Aß exist, such as "[…] monomers, oligomers, protofibrils, and insoluble fibrils in plaques" [68]. An effective treatment is the removal of oligomers and protofibrils as they have been indicated to be toxic. Lecanemab, aducanumab, and gantenerumab were assessed concerning their binding properties to diverse Aß species and showed different binding profiles in a recent study. All of them showed a low affinity in binding monomers with gantenerumab displaying a stronger affinity. Compared to fibrils, a tenfold stronger binding of lecanemab to protofibrils was found. In contrast, gantenerumab and aducanumab favored fibrils over protofibrils [68]. In a recent study published in 2023, solanezumab was assessed in its ability to target preclinical AD. In individuals with elevated amyloid levels in the brain, it is supposed to target monomeric amyloid, though it did not slow cognitive decline over a period of 240 weeks compared to the placebo group [69]. In a two-phase three multicenter randomized double-blind placebo-controlled study investigating crenezumab in individuals with pre-stage AD, 60 mg/kg crenezumab or a placebo was given intravenously to the participants every four weeks for up to 100 weeks. Despite positive toleration of the intervention, no reduction in clinical decline could be shown in individuals with early AD [70].

Recent research in concordance with the genome-wide association studies (GWAS) has identified four loci for pTau and two loci for Aß42 with both showing the strongest association for Apolipoprotein E (APOE). APOE ε4 appeared to lower amyloid beta levels and increase

levels in pTau, whereas APOE ε2 showed opposite effects [71-73]. With so far being the only loci with an overlap concerning the two proteins, partly various genetic backgrounds are assumed for the two pathological hallmarks [73]. APOE ε4 carriers were found to have a 4 to 5.5 years difference in median age when it comes to the onset of AD [74]. In conclusion, the APOE ε4 allele has been described as the strongest genetic risk factor, when it comes to the development of sporadic AD, whereas the APOE ε2 allele is the strongest genetic protective factor. While numerous mouse models expressing human APOE alleles were successful in researching therapeutic approaches, the translation to clinical trials with human individuals constitutes a challenge so far [75]. However, the research on drugs and therapies is ongoing and develops constantly.

Furthermore, dietary interventions, physical exercise, cognitive training, and lifestyle changes have received increasing interest as conservative treatments in the past years. Various studies show that positive changes in lifestyle and vascular risk control may decelerate the progression of cognitive impairment [76].

3.2.1. Hypotheses on the Aetiology of AD

AD is recognized as a global public health priority by the World Health Organization [77]. Therefore, research has come up with various hypotheses around its aetiology: the cholinergic hypothesis, the Aß hypotheses, the inflammation hypothesis, etc. [78]. This last hypothesis has gained considerable attention in the past years, as research has shown that inflammation plays a pivotal role in the pathogenesis and progression of AD. As the inflammation theory currently seems to be the most accepted hypothesis due to the increasing research on it, the following will be based on this hypothesis. “The accumulation of Aβ causes microglia activation, recruitment of astrocytes, and increased generation of pro-inflammatory cytokines […] such as interferon gamma (IFN-γ), interleukin (IL-1β) and tumor necrosis factor alfa (TNF-α) […]” [79]. The inflammatory process in the central nervous system (CNS) in its acute response is a self-defence mechanism attempting to get rid of damaging stimuli and restoring the integrity of the tissue. If this process becomes chronic, it is called neuroinflammation in an acute or chronic variant and may be harmful to the body. The activation of neural endothelial cells could also play a role in the process of neuroinflammation. This might in turn at least partly explain the increased production of Aß42 oligomers astrocyte, which are described as senile plaques and considered one of the major hallmarks of AD besides neurofibrillary tangles, by -neurons [25]. Thus, if the inflammation does not resolve, it may turn into a cycle of neuronal damage, as seen in AD and its chronic state of inflammation [80].

Considering the risk factors that potentially influence the pathophysiology of AD, models assume that the reduction of the aforementioned factors might prevent 33% of AD worldwide [22,81]. This leads research to concern inself with the influence of lifestyle changes in the context of AD aetiology and prevention. A great number of studies have shown that obesity increases the risk of developing late-onset dementia [79]. Other research has found an interrelation between obesity and a low-grade chronic inflammation [79]. “Monocyte-derived macrophages and adipocytes in adipose tissue produce pro-inflammatory cytokines, such as IL-6, IL-1β, TNF-α and induce secretion of acute-phase protein, such as CRP [c-reactive protein]” [79]. Another noteworthy aspect is that obesity correlates with other risk factors influencing dementia, such as dyslipidemia, hypertension, atherosclerosis, insulin resistance and type II diabetes mellitus (T2DM). Talbot et al. suggest that the pathophysiology of AD and T2DM is similar. Both conditions show a disorder when it comes to carbohydrates, and are associated with insulin resistance, inflammation, oxidative stress (OS) and a decline in cognitive features. Individuals with T2DM show a risk of developing AD at 50-100%, as T2DM correlates to a brain insulin resistance [82].

Furthermore, elevated cortisol levels have been linked to Aß pathology through [^{11}C] Pittsburgh Compound-B (PIB)-PET and serum Aß1-42. Those elevated levels were shown in several biofluids, such as in the CSF, serum, plasma, saliva, and urine. Moreover, cortisol levels have been suggested to mediate adverse effects of Aß concerning cognition in older healthy individuals with an elevated level being associated with worse memory performance [83].

There are not only negative associations when it comes to diet. More and more research shows that it may be a tool to modulate the risk factors of AD. As described above, inflammation is associated with a list of factors that lead to various health concerns, which supports an association between cognitive decline and highly inflammatory diets reasonable [84,85]. In this context, animal studies have shown that cognition may be enhanced through food and its associated hormones. These studies have also demonstrated an effect on memory by various nutrients, such as blueberries, olive oil and docosahexaenoic acid (DHA) [86]. An interrelation between a decrease in cognitive decline, incidences of AD and a Mediterranean diet (MeDi) has been established thus far [86]. “The Mediterranean Diet is described as including high intake of fruits, vegetables, wholegrains, nuts; moderate intake of fish, poultry and alcohol (particularly red wine, with meals) and low intake of red and processed meats with olive oil used as the main fat source” [87]. Neurodegeneration and its inflammatory process seem to be reduced through the nutrients consumed in the MeDi [88,89]. Furthermore, the MeDi might also reduce the aforementioned process by modulating the gut microbiome and circulatory

pathways [88]. Even though the protective aspects of this diet and its mechanism are not yet fully understood, it is assumed that the aspects leading to an improved cardiovascular health might also slow the process of neurodegeneration. A substantial change in dietary pattern and a switch to a healthy dietary composition yields the greatest benefits [85]. The dietary approach has been successfully implemented in various fields of medicine, for example, the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) [86,88,90]. MeDi and DASH share similarities in their food category recommendations, though DASH promotes the use of low-fat dairy foods, low sodium and no alcohol. Research has assessed the relation of dietary intervention with delayed cognitive decline as well as protection against neuronal degeneration [88]. In combination with other nutritional factors, these diets could be used to support treatment of or even prevent medical comorbidities associated with cognitive decline and AD [91].

The following provides a bridge over from the inflammatory theory to the concept of OS, as a linkage of those two components is of current interest in the research field [92].

3.2.2. Oxidative Stress

The human brain only makes up 2% of the body weight, but its functional units, the neurons, use up to 20% of the oxygen supply provided for the entire body. Thus, neurons are more susceptible to OS and damage due to their higher metabolic rate compared to other cells [93]. The concept of OS was introduced in the research field of redox biology for the first time in 1985. Since then, a wide field of research has opened and developed. Despite the vast development in this area over the past decades, no specific definition of oxidative stress has been formulated until now [92]. “Over time, the mechanistic basis of the concept was largely forgotten and instead of the oxidative stress hypothesis becoming more precise in terms of molecular targets and mechanism, it became diffuse and nonspecific” [94]. The original description of oxidative stress is “[a] disturbance in the prooxidant-antioxidant balance in favor of the former” [95]. An updated version describes it as “[a]n imbalance between oxidants and anti-oxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage” [96]. Due to the extensive variety of compounds, research strived to introduce sub forms of OS as well as intensity scales ranging from low physiological OS to excessive and toxic oxidative burden [96,97].

Closing the link to neurodegeneration and associated degenerative diseases, OS in the deregulation of redox balance shows a strong association to those mechanisms as the brain

is more susceptible to them because of chemically diverse reactive species being harnessed to execute heterogeneous signalling functions [98]. Considering age-related cognitive decline and neurodegeneration, the significant role of oxidative distress and eustress indicates the benefit of nutrition and antioxidant micronutrients in neuroscience [99,100]. To understand the nutritional cognitive neuroscience further, the multifactorial, heterogenic and extremely complex pathophysiology of brain-aging must be appreciated, while acknowledging that age remains the main risk factor for AD [101-103]. The CNS is dependent on oxygen levels and especially sensitive when it comes to changes in those levels, as well as to a rise in reactive oxygen species (ROS), derivates of molecular oxygen. Therefore, 'oxidative distress' is described as an arrangement of different ROS, which leads further to molecular damage. By contrast, 'oxidative eustress' portrays a state of balance between ROS at their physiological levels and their redox signaling function via various post-translational modifications [100].

OS is one of the major factors conducive of neurodegeneration. Additionally, further research has detected irreversible damage in nucleoid acid functioning and protein structure through OS [99,104]. Recent findings in research concluded that the reduction of homocysteine through vitamin B supplementation and the intake of dietary antioxidants may reduce the OS damaging the brain [23,87]. These and additional anti-inflammatory components will be discussed further in the following chapters.

3.2.3. Anti-inflammatory Components

3.2.3.1 Nutritional Factors

Fatty acids

Due to the brain's high demand for energy, high consumption of oxygen and profusion of easily peroxidable polyunsaturated fatty acids (PUFAs) and further aspects, it is greatly susceptible to oxidative imbalance [105]. Therefore, unsaturated fatty acids and saturated fatty acids (SFAs) might constitute risk factors for various diseases if consumed in an inappropriate amount [106]. Furthermore, cognitive impairment may be increased through high intakes of SFAs. In contrast, components of the omega-3 group, such as monosaturated fatty acids (MUFAs) and PUFAs, might lead to a lower risk of dementia if consumed in higher doses [107,108]. Polyunsaturated fatty acids function as neuronal building blocks, while their chain lengths and their number of double bonds define the attributes of the fatty acid. Therefore, MUFAs and PUFAs function as antioxidative components. Research has shown that a high dietary intake in MUFAs prevents a decline in cognitive functioning as well as promoting better insulin sensitivity and postprandial glycaemia [109]. Additionally, ingestion of PUFAs plays a crucial role for the body due to the inability of the human body to synthesize them, especially the alpha-linolenic acid (ALA) belonging to the omega-3 and the linolenic acid (LA) to the omega-6 group [110,111]. LA is needed for the synthesis of arachidonic acid (AA) and ALA for longer chain components, such as eicosapentaenoic (EPA) and docosahexaenoic (DHA) acid [110,111]. An optimal balance between the omega-3 and omega-6 fatty acids is of great importance, as a minor imbalance may disturb the function of the nervous tissue. Raised cell aggregation through AA deranging DHA from membrane phospholipids may even lead to production of neurotoxic metabolites and pro-inflammatory cytokines [112]. In general, it has been shown that an adequate dietary intake of DHA helps prevent the formation of amyloid-ß deposits and neurodegenerative processes, possessing protective properties against AD development and progression of associated brain atrophy [106,113]. Considering antioxidant components, DHA derivates work against free oxygen radicals by eliminating their toxic effects as well as protecting against apoptosis and neuronal damage [114,115]. Data shows that DHA supports the dendritic branching and axonal extension through the promotion of neuronal development and additionally it's enhancing the formation of new synapses. In the context of AD, disturbances in DHA synthesis may occur because of a decrease in enzyme activity through aging, leading to misfunctioning of the nervous system [111].

Curcumin

Research has shown that polyphenolic curcumin, derived from turmeric, might have positive effects during the MCI stage. In contrast, no significant difference was found between the cognitive performance of patients with AD supplementing a placebo or treatment with curcumin [116]. Further studies have shown that curcumin may have an effect on chronic inflammatory process in the brain by influencing Aß protein plaques [117]. Moreover, in vivo studies did not only find a preventative effect of curcumin in the aggregation of new deposits but also a reduction of already existing plaques [118,119]. In addition, a decrease in oxidized protein concentration and a reduction on OS levels was observed [117]. Furthermore, curcumin inhibits cyclooxygenase 2 (COX-2), the nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-κB) signaling as well as of the pro-inflammatory cytokine IL-6 and IL-1ß [120,121]. Therefore, it might have a more positive effect on the process of inflammation in combination with omega-3 fatty acids, such as EPA und DHA [120]. In conclusion, it can be said that through the knowledge collected so far, the synthesis of various forms of curcumin could be a useful drug and tool concerning AD diagnosis and treatment [122].

Coffee and caffeine

With coffee being an integral part in the societal lifestyle today, its interplay with dementia risk is of particular interest. In middle-aged population, 3-5 cups of coffee per day already decrease the risk of dementia or AD by 64% [123]. Therapeutic effects have been established, recommending the intake of approximately 500mg of caffeine to induce neuromodulatory and neuroprotective properties. Animal studies have shown decreasing amyloid-ß levels in the brain through inhibition of synthesizing enzymes [124].

Caffeine has a bioavailability of nearly 100%, reaching its peak plasma concentration after 40 minutes and penetrating the blood-brain barrier quickly [110]. Additionally, caffeine possess various anti-inflammatory properties and antioxidative qualities, such as the inhibition of microglial reactivity, a reduced infiltration of immune cells and a decreased amount of inflammatory cytokines in the hippocampus in correlation with the plasma caffeine concentration [125]. In a summary of 15 human studies, an association was suggested between caffeine intake and a lower risk of cognitive disorders including cognitive decline, cognitive impairment and AD, despite the presence of some inconsistent results [126].

Resveratrol

Resveratrol, a compound of the polyphenolic family, possesses various promising aspects and effects, which might aid in the protection against neurological diseases. Its effects are anti-viral and anti-inflammatory, and it has antioxidative aspects, aiding in the activation of antioxidative enzymes. Furthermore, with the inhibition of amyloid-ß aggregation in the hippocampus, resveratrol poses a promising variable in the prevention of AD [127-129]. It is assumed, that the supplementation of resveratrol might improve different measures of cognitive performance [130]. However, a number of negative symptoms were observed when supplementing resveratrol as well. These include hyperplastic changes of the kidneys and gallbladder if given in a high dose, as well as vomiting, diarrhea, leukocytosis and a decrease in erythrocytes, hemoglobin, and hematocrit, as resveratrol can penetrate the brain blood barrier (BBB). Still, a supplementation of a low dose of 0.3 g/kg bodyweight/day for 4 weeks did not show any side effects [127,128].

Overall, it can be said that resveratrol might endorse brain resilience to the deposition of amyloid via possibly maintaining the integrity of the BBB through the reduction of cerebrospinal fluid biomarker MMP9 and induce adaptive immune responses. Therefore, cognitive decline might be slowed down in patients with AD through a central and peripheral immune response, which might also arrest neuron death [131].

Microbiota

It has been shown that an anti-inflammatory effect on the digestive system induced by probiotic bacteria may be beneficial in various aspects. Microbiota keep the intestinal barrier intact and prevent pro-inflammatory components from infiltrating the bloodstream. These inflammatory components, which comprise chemokines, interleukins, and cytokines, contribute to the inflammatory process and may be involved in aetiology of neurological diseases [132,133]. If a dysbiosis exists, the components readily get into the bloodstream via the reduced microbiotic gut lining cross the BBB, which leads to a release of additional compounds and affect the pathogenesis of AD [134,135].

Additionally, studies in humans have shown that one of the initiating causes of AD could be a bacterial or viral infection. For instance, in people suffering from AD with an additional chronic Helicobacter pylori infection, the release of inflammatory mediators is triggered and a reduced score in the Mini-Mental State Examination (MMSE) can be found compared to non-infected persons [136,137]. Furthermore, higher levels of Aß40 and Aß42 can be found in the serum of AD patients who suffer from an infection by Helicobacter pylori as well as other bacteria [137,138].

3.2.3.2 Carotenoids

Moving on from the more commonly known nutritional factors, some nutritional biomarkers like the serum antioxidant vitamins, carotenoids and retinoids also display associations with AD [139]. The dietary intake of antioxidants has been to possibly reduce ROS and therefore ease oxidative DNA damage [140]. In conclusion, a protection against cognitive decline and overall neurodegenerative processes can be assumed [141].

Carotenoids and retinoids, which specifically are vitamin A derivates and are involved in axon outgrowth and neural patterning and differentiation, are noteworthy when talking about aging due to their comparable biological features, such as inhibition of malignant tumor growth, induction of apoptosis, and, most importantly, antioxidant properties [142,143]. Their colorful liposoluble pigments can be found in fungi, bacteria, plants, and algae as well as in various fruits and vegetables [144,145]. Of the more than 600 carotenoids, only around 40 appear in typical human diets [146-148]. Approximately 20 of these carotenoids were identified in human blood and tissue and comprise lutein, cryptoxanthin, lycopene, α-carotene and β-carotene [146-148].

The basic composition for most of the carotenoids is a central carbon chain with an alteration of single and double bonds and various cylic or acyclic end groups [149]. These structures can be separated into non-provitamin A and provitamin A compounds (e.g., α-carotene, β-carotene and β-cryptoxanthin) [149]. Another way of classifying these components is through their functional groups. The first group can be identified through xanthophylls, with oxygen as their functional component (e.g., lutein and zeaxanthin). The second group are the carotenes, which do not possess any functional group and only have a parent hydrocarbon chain (e.g., lycopene, α-carotene, and β-carotene). Other derivatives such as apocarotenoids (e.g. vitamin A, retinoids, α-ionone and β-ionone aromatic volatile compounds) exist through carotenoid cleavage dioxygenases being used by oxidavtive cleavage [150].

In figure 3 below, the biosynthesis is shown for a clearer visualization of the micronutrients used in the main paper. Those specifically are underlined in figure 3.

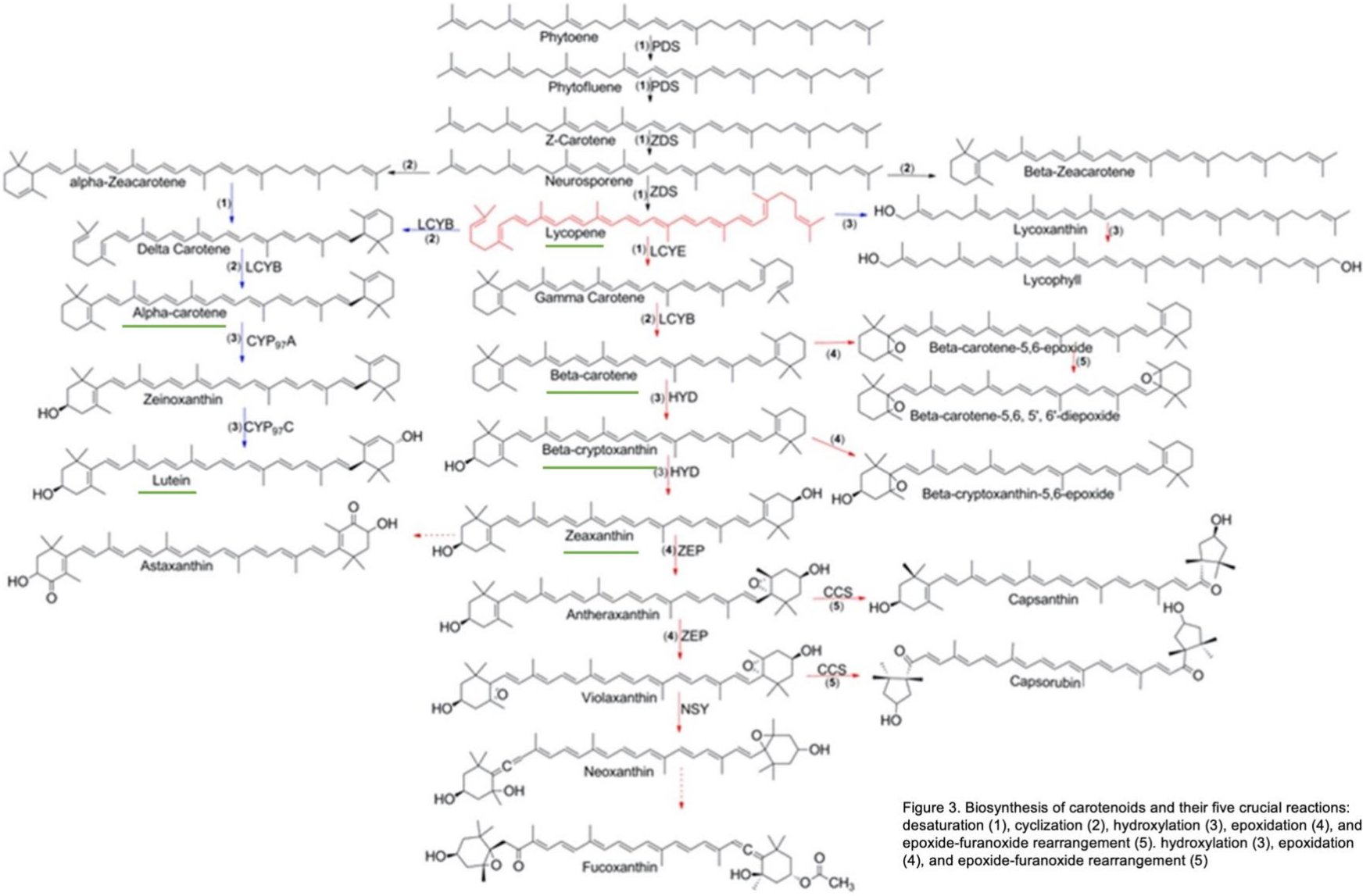

Figure 3. Biosynthesis of carotenoids and their five crucial reactions: desaturation (1), cyclization (2), hydroxylation (3), epoxidation (4), and epoxide-furanoxide rearrangement (5). hydroxylation (3), epoxidation (4), and epoxide-furanoxide rearrangement (5)

The benefits of the carotenoids are mostly attained through their antioxidant effects as a main scavenger of ROS, while pathological processes and aerobic metabolism occur, reactive oxygen and nitrogen species are produced and play a major role in the process of degenerative diseases [146,149]. “Carotenoids can scavenge radicals in three steps: electron transfer (oxidation, reduction: CAR + ROO → CAR^{+} + ROO^{-}), hydrogen abstraction (CAR^{+}- ROO → CAR + ROOH) and addition (CAR + ROO → ROOCAR)” [144].

Free radicals can be neutralized through these compounds accepting electrons from reactive species, which is being possible through the presence of conjugated double bonds [148]. Furthermore, synergistic effects of scavenging reactive nitrogen species and the inhibition of liquid peroxidation may be accomplished through combining two lipophilic antioxidants [149]. Overall, it has been suggested that when different compounds with alterable antioxidant activity interact with each other, an additional protection is given against increased OS [151]. These carotenoid mixtures were assessed for their antioxidant activity in multilamellar liposomes, showing that combinations were more effective than only using the singular compound when it comes to the inhibition of liquid peroxidation [149,152].

In conclusion, a list of the micronutrients used in the main paper is shown: lutein, zeaxanthin, cryptoxanthin, lycopene, α-carotene, β-carotene, α-tocopherol, γ-tocopherol, and retinol.

3.2.3.3 Antioxidant Vitamins

Vitamin A

As mentioned in the chapters above, inflammation plays a pivotal role in the aetiology of acute and chronic neuropsychological diseases. Microglial activation might be one of the central causes of AD, which is elicited by a characteristic mechanism observed during high levels of inflammation. Furthermore, the local concentrations of retinoic acid could be altered through the malfunction of the microglia [153]. The brain converts vitamin A to retinoic acid and consecutively the retinoic acid receptors get activated, which regulate transcription as well as control nongenomic actions in the cytoplasm. For the regulation of synaptic plasticity concerning especially the learning and memory areas of the brain, a controlled synthesis of retinoic acid is crucial [153].

Carotenoids possess one beta ionone ring and are precursors of vitamin A, which quite possibly contribute to the human vitamin A supply. β-carotene being the only carotenoid due to its structure that can split into two molecules of all-trans-retinal [76]. The enzyme ß-carotene-15, 15'-oxygenase (BCO1) catalyzes the cleavage of the central double bond using substrates like lycopene, α-carotene and other apo-carotenals [154]. Recent research has confirmed the preservation of the enzymatic activity of β-carotene-oxygenase 2 (BCO2) in the human body, which transforms the carotenoids into more polar metabolites. BCO2 plays a role in the regulation of the carotenoid homeostasis and can be found in the human retina in high levels. The enzyme has been shown to be an effective protector from OS for human cell lines. Furthermore, a control of the transcription of genes associated with embryonic development, cell proliferation, differentiation and apoptosis is given, if the retinoic acid receptor/retinoic X receptor dimer is formed [155,156].

A cross-sectional study has found that a low intake of vitamin A may be associated with an increased risk of dementia [157]. In 2020, a study showed that a higher β-carotene intake may decrease the risk of cognitive impairment [158]. Finally, it can be said that a deficiency in vitamin A leads to a deterioration of the functions of synaptic plasticity concerning learning and memory regions in the brain and therefore a failure in the signaling of retinoic acid may be associated with cognitive decline with normal aging but also with AD [153].

Vitamin B

After the discussion of how antioxidant-rich nutrition may influence neurocognitive degeneration, this section focuses on the components involved in the metabolism of homocysteine. As the demethylated derivative of methionine, homocysteine can either be

metabolized in methionine or cysteine. For these processes, the vitamins B2, B6, B12 and folic acid are required as cofactors. If a deficiency in vitamin B6 and B12 or an overload of methionine is present, the trans-methylation of homocysteine to methionine is disturbed and results in hyperhomocysteinemia. Therefore, monitoring of the concentration of the neurotoxic homocysteine is crucial in the prevention and further in the treatment of AD [108,159].

Even small increases of the concentration of homocysteine in the blood serum by 5μmol/L may lead to atherosclerosis of large blood vessels, potentially causing an ischemic stroke [123]. In the context of AD, inflammation may be induced or even increased by elevated levels of homocysteine which may lead to cognitive dysfunction through the promotion of tau protein phosphorylation, a raise in the concentration of amyloid-β precursor protein and an aggravated amyloid-β pathology [123].

An exemplary study on the outcome of B group vitamin supplementation showed that in 266 participants with MCI over the age of 70 years had a 30% lower concentration of homocysteine compared to the placebo group. Especially among participants with homocysteine above the median baseline of 11.3μmol/L, a significant benefit concerning B-vitamin treatment was shown [160]. Patients undergoing supplementation involving 0.5 mg vitamin B12, 20 mg vitamin B6 and 0.8mg folic acid for 2 years were able to accomplish better results in the MMSE and tests targeting the semantic and episodic memory [160].

Whereas various other studies came to the same conclusion [161], the relationship between AD and homocysteinemia has not been explored fully, but an elevated dietary intake of folic acid, vitamin B6 and B12 might pose a form of protection for the nervous system and thus decreasing the risk of AD development [159,162].

Vitamin C and E

Vitamin C is one of the key antioxidants of the CNS. It works as a scavenger of ROS and reduces β-amyloid activity. Additionally, it protects against tocopherols through regenerating them from their radical form [162,163]. The daily intake of vitamin C should be 75mg in men and 50mg for women. A higher dietary intake of vitamin C, for example in strawberries, can possibly help reduce AD, which has been confirmed in a prospective study with 925 participants. Over the mean follow-up of 6.7 (±3.6) years, 245 participants have developed AD [164]. The results showed that a higher intake in strawberries was associated with a reduction in the risk of sickening from AD (HR = 0.76, 95% CI: 0.60–0.96) [164].

Vitamin E (tocopherol) is among the most potent lipophilic antioxidants and prevents the oxidation of unsaturated fatty acids by disrupting the production of free superoxide radicals [162,165]. These fatty acids are important components of cell membrane construction [162,165]. Lipid peroxidation and ß-amyloid deposition can be reduced through vitamin E when stored in the CNS [165]. The results on vitamin E are still inconclusive so far. Mangialasche et al. published the following findings: “Patients with mild cognitive impairment (MCI, n = 166) and people diagnosed with AD (n = 168) have been shown to have significantly lower total tocopherols (6.80 µmol/mmol cholesterol and 6.40 µmol/mmol, respectively), total tocotrienols (97.28 nM/mmol cholesterol and 91.33 nM/mmol cholesterol, respectively) and total vitamin E in the blood (6.9 µmol/mmol cholesterol and 6.49 µmol/mmol), compared to persons with normal cognitive abilities (CN, n = 187), whose total tocopherols were 7.67 µmol/mmol cholesterol, total tocotrienols—118.02 nM/mmol cholesterol, total vitamin E—7.8 µmol/mmol cholesterol” [161,166]. The recommendations for vitamin E are set at 10μg of retinol equivalent/day for men and 8μg for women [167].

The relationship between cognitive ability and fruit and vegetable consumption (400g) has been assessed in a 13-year study in a group of 2533 participants between the ages of 45 and 60 years. The results showed that products rich in vitamin C and E appear to be positively correlated with the data of verbal memory tests, in divergence to the consumption of vegetables rich in ß-carotene [168]. Comparable observations were made in another study that assessed the effects on the cognitive function of 256 participants with MCI at the age of 60 to 75 years through supplementation with 300 mg of vitamin E and 400 mg of vitamin C. After a year of intervention, though the cognitive abilities did not improve, a reduction of OS of the body could be observed [168].

Vitamin D

Vitamin D has been shown to play a significant role in the development of neurodegenerative diseases. It is a hormone that possesses neurosteroid-like properties and can bind onto vitamin D receptors (VDR). The vitamin has a broad spectrum of properties, ranging from the commonly known role in the calcium metabolism, to its role in the cell cycle control, the modulation of the immune system, protection against cancer and cardiovascular diseases, to the regulation of cognitive and neuromuscular functions. In earlier studies, decreased levels of VDR mRNA were found in the hippocampal cells of AD patients. Later studies have shown imbrications of amyloid pathology mechanisms and vitamin D action in cortical or hippocampal neurons. Therefore, decreased vitamin D levels seem to influence or even change the microenvironment of the brain and enhance the pathogeneses of AD or instigate amyloid aggregations directly. These changes lead to a negative feedback loop by altering the vitamin

D related pathways before AD symptoms appear. Thus, research on the molecular mechanisms of vitamin D in terms of neuronal development and neurodegenerative diseases, in amyloid beta clearance by macrophages and glia, has found valuable data[169], leading to more questions concerning neuronal development and survival and demand a focus on its matter in the future [169].

3.3. Change in Cognitive Function during Aging

As discussed in the previous chapters, the complex but normal process of aging is a progressing decline in physical functions which leads to physical and cognitive impairment [170]. Aging entails a number of biological changes which lead to a decline in ADLs [171].

Cognitive reserve (CR) plays an important role in this process. It describes an adaptability of cognitive processes that assists in elucidating differential susceptibility of cognitive abilities or daily functions to brain aging, insult or pathology [172]. This concept indicates that occupational attainment, general cognitive ability, and experiences causing social, physical and cognitive stimulation might enable cognitive processes to be resilient if combined or interacting with genetic features. Enforcing this resilience may influence the capacity, flexibility or efficiency of brain networks, leading to improved physical functioning in regard to brain disease or aging [173]. By contrast, the concept of **brain reserve** refers to the structural aspects of the brain at various points in time. When functional and cognitive decline arises, the threshold for functional impairment is impacted through brain reserve and is therefore possibly protecting against age and disease-related brain changes [173]. Furthermore, **brain maintenance** describes the procedure of maintaining or enhancing the brain morphology by the aforementioned lifetime experiences in combination with certain genetic factors [173]. Two further mechanisms are important regarding the study of preclinical AD: resistance and resilience. **Brain resistance is** the brain's ability to resist pathology in an underlying process and may be measured by non-detectible or lower pathology of AD than expected [172,174]. "**Brain resilience** is defined as the ability to cope with AD pathology and is measured by better-than-expected cognitive performance, brain structure, or function given some level of AD pathology" [172,174]. Brain maintenance and brain resistance can be said to be similar according to Stern et al. They also pose that cognitive reserve and brain resilience overlap [172,175].

Research has identified various structural and functional brain changes caused by aging, which has led to the establishment of theories on their association with neurocognitive changes. A very noteworthy point is the decrease in grey matter volume. Atrophy is predominantly found in the prefrontal cortex and, to a lesser extent, in the temporal lobes and in the hippocampus [176]. There are numerous theories on potential causes. One of them postulates the death of neurons themselves, which creates an opportunity for the accumulation of mutations through infrequent cell division [177]. A possibly better explanation for this loss in volume might be the decrease in the number of connections and the size of the neurons [178,179]. With the process of aging, neurons go through morphological changes, which include a

decrease in neurotic spines and the increasing complexity of dendrite arborization and dendrite length [180]. Therefore, those morphologic changes possibly play a part in the reduction of synaptic density [180].

In connection to AD, the protein beta-amyloid accumulation in the brain plays an important role in the pathological process of the disease. It has been proposed that the combination of patients with MCI and an elevated presence of these proteins might predict AD development [181-183]. The same theory might apply to cognitively normal individuals as a presence of beta-amyloid was found to predict a higher eventuality of developing AD [181-183].

An interesting point is that the decrease in white matter volume is far greater than the one in grey matter volume [184]. Various studies have investigated these changes and described them as a decrease in parahippocampal white matter leading to decreased communication with structures of the hippocampus [185], indicating a possible mechanism that might contribute to age-associated memory decline [185]. Additionally, a functional change has been identified. A decline in white matter integrity was observed by using diffusion tensor imaging: the relevant areas concerning white matter decline showed white matter in the anterior corpus callosum, superior longitudinal fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus, (anterior) thalamic radiation and the cingulum and further displayed an association with shortfalls in executive function [186,187].

Various neurocognitive changes occur during and due to the process of aging, which will be explained briefly in the following paragraphs. Firstly, some important terminology will be introduced. The term **crystallized intelligence** can be described as knowledge, abilities and skills that are familiar, well-practiced and overlearned [188]. This intelligence is built upon the collection of information throughout one's life experiences [189]. General knowledge or vocabulary are examples of crystallized abilities, and improve particularly throughout the sixth and seventh decade of life [190]. **Fluid intelligence** describes abilities concerning reasoning about unknown fields of knowledge or that are not familiar. The ability to attend to and manipulate one's environment, to learn and process new information and solve problems describes the trajectories of fluid intelligence [189]. Its domains includes memory, psychomotor ability, processing speed and executive function [190]. Both concepts, crystallized and fluid intelligence, are patterns of cognitive change that happen over the lifetime [188].

Executive function implies a wide range of abilities, such as planning, organizing, mental flexibility, self-monitoring and problem-solving. This function can be described as the capacity that enables a person to engage in appropriate and independent behavior successfully. After

the age of 70, a decline may be identified in mental flexibility, abstraction and concept formation [188]. If a speed motor component is required in an executive ability, those particular executive abilities are extra vulnerable to aging [191]. Moreover, the ability to inhibit an automatic response to promote the creation of a novel response, called response inhibition, may be affected [192]. Progressing age also shows a decline in the ability to reason with unfamiliar information. In contrast, the reasoning about familiar material, the capacity to appreciate similarities as well as the capacity to describe the meaning of proverbs stay constant throughout life [193].

Visuospatial abilities have to do with understanding a space in two and three dimensions [194]. These abilities persist throughout a person's lifespan and include spatial perception, the capacity to appreciate the physical location of objects alone or in relation to each other and the ability to identify familiar objects [193]. The abilities associated with assembling individual parts to make a fitting whole are called visual construction skills and decline with increasing age [194].

Language skills remain persistent with aging, as well as the vocabulary, which even improves with progressing time. This domain is constituted by crystallized and fluid cognitive abilities [191,195-197]. Verbal fluency is the ability to accurately look for and produce words belonging to a specific category in a certain amount of time [196,198], which does show a decline due to aging. Visual confrontation naming has been shown to hold up until the age of 70 with a following decline in the years afterwards [199].

The loss of memory is by far the most common complaint when it comes to the aging population [200]. These changes in memory might be caused by an interplay of various factors, such as a decline in the ability to filter irrelevant information [200], a slower speed of processing [201] and decreased practice to improve memory and learning [202-204]. The two main types of memory are the nondeclarative and the declarative memory.

The nondeclarative memory, also described as the implicit memory, is outside of the person's awareness. The memory for motor and cognitive skills portrays a part of the implicit memory, called procedural memory. Additionally, the nondeclarative memory remains unchanged over the lifespan [188,193].

Declarative memory, also known as explicit memory, includes episodic and semantic memory. It is characterized by the recollection of events and facts in a conscious way. Episodic memory contains personally experienced events at a precise time and place and may be accessed through figures, stories and word lists. Practical knowledge, language use and fund of information are components of semantic memory. With the process of aging, a decline in both

components may occur, even though the semantic memory has been shown to decline later in life than the episodic memory, which shows a gradual lifelong decline [205].

Attention can be described as the capacity to focus on stimuli [188]. Selective attention is the skill to concentrate on specific things, filtering out any irrelevant information. This skill is important when driving in a car or trying to hold a conversation whilst in a noisy environment [193]. Divided attention, also known as multitasking, is the trait to concentrate on multiple tasks at the same time. Studies have shown that older adults perform significantly worse than younger populations when using their working memory, like calculating a tip on a restaurant bill [200]. A slow decline in the simple auditory attention span in later life was observed [188]. More difficult tasks, like divided and selective attention, show a more noticeable effect on decline through age [206,207].

Processing speed includes the speed in which motor responses and cognitive activities are accomplished. In the third decade of life, a decline in this capacity may be observed, which continues throughout the remaining lifetime [198,206,207]. A slower processing speed influences many cognitive changes and possibly affects the individual's performance on neuropsychological tests, even on those which are designed to evaluate different cognitive domains (e.g., verbal fluency) [193].

3.4. Lifestyle and Endothelial Function

In 2003, Vagnucci and Li suggested that inflammation, cerebral hypoperfusion, gene polymorphisms and molecular lesions might act as possible mechanisms of AD [208]. Evidence has been mounting the association of neurovascular dysfunction to AD in recent years. Cerebral dysfunction might play a major part in the onset and progression of cognitive decline, possibly contributing to the development of AD. Various components, that are still being researched, may contribute to this development. Therefore, numerous mechanisms, such as vascular degeneration, vascular changes and further including cerebral hypoperfusion and the accumulation of Aß-protein with an impaired clearance across the BBB are considered by the researchers. A negative effect on the synthesis of proteins unfolds through a decrease in cerebral blood flow (CBF), potentially also negatively affecting the capacity for learning and memory [209,210]. Further, Aß-protein accumulation may occur in the brain parenchyma and on the blood vessel linings. If this process occurs in the cerebral blood vessels, it is called cerebral amyloid angiopathy (CAA), one of the hallmarks of AD and associated with cognitive decline. Through CAA, intracerebral bleedings may occur to different extents and may increase inflammatory responses as well as neurodegenerative processes [209,210]. In the following, a short review of important structures and mechanisms will be described.

The **neurovascular unit (NVU)** comprises three different cell types: 1. **vascular cells**, such as the endothelial cells of the brain, vascular smooth muscle cells (VSMC) and pericytes; 2. **glial cells**, such as oligodendroglia, microglia and astrocytes; 3. **neurons**; efficient cell-to-cell cross-communication is provided through the proximity of the neurons and the non-neuronal neighboring cells and is crucial for efficient functioning of the CNS. The tasks of the NVU consist of deactivating neurotransmitters, signaling via anioneurins, matrix interactions and BBB permeability, controlling neurovascular coupling and clearing toxins from the brain [210]. The tunica adventitia (running nerves, fibroblasts, and collagen), tunica media (mostly VSMC) and tunica intima (endothelium) make up the three layers of cerebral arteries [209]. CBF can be controlled through the VSMC [211], which is of great importance for the maintenance of the NVU [209]. In conclusion, for a healthy brain and proper functioning and communication, especially for neuronal synapses and circuits to maintain normal cognitive function, of the cells of the NVU are essential [209].

The **BBB's** function is to prevent plasma components, like leukocytes, and red blood cells from entering the brain through its continuous endothelial cell membrane. It also maintains the constant "chemical" configuration of brain's interstitial fluid, contributing to optimal brain

function. For the matter of proper neuronal and synaptic function, the BBB works as a regulation tool using specific transporters in the endothelium of the brain to regulate delivery of required energy metabolites and essential nutrients. Together with pericytes, the BBB also clears the brain of vasculotoxic and neurotoxic macromolecules, which control the blood entry [212].

Moving back to CAA, recent research has shown that vascular changes play a pivotal role in the pathogenesis of AD and other forms of dementia [213]. Focal degenerative changes in the brain microcirculation have been observed in various forms of dementia. This is hypothesized to be caused by different mechanisms, such as reductions and atrophy in the capillary network, leakage of blood-derived molecules, loss of BBB tight junction proteins, accumulation of perlecans and collagen in the basement capillary membrane, loss of mitochondria and a rise in endothelial vacuolization [210]. CAA is seen in 80% of AD patients and may be caused by the accumulation of Aß and its subsequent deposition in the intracerebral and pial arteries [214,215]. As a consequence of the atrophy in the VSMC layers of smaller arteries in AD patients with CAA, this Aß deposition may lead to a rupture of the vessel walls and subsequent intracerebral bleeding, potentially causing an exacerbation in dementia [210].

Various forms of brain imaging, such as transcranial doppler measurements, MRI and single photon excitation computed tomography (SPECT), have revealed that the resting CBF is significantly lower in patients with AD and therefore might constitute an early event in the pathogenesis [216]. Additionally, in these specific patients, a cerebral hypoperfusion has been established through arterial spin-labeling MRI [216]. Furthermore, patients with MCI seem to have a delay in CBF response while performing a task evaluating episodic memory. Functional MRI using blood oxygenation level-dependent contrast was used to asses increases in CBF and showed an even more significant delay in patients with AD [217]. This might lead to the assumption that a reduction in the CBF can already be found in the early stages of AD, such as MCI [209]. Another investigation comprised the cerebral glucose transport across the BBB using 2-[18F] fluoro-2-deoxy-D-glucose PET, which revealed that the individuals with a prior stage to AD showed a reduction in cerebral glucose uptake [218,219]. These findings suggest that these changes in metabolic processes may not be resulting from atrophy of the brain but preceding the process of neurodegeneration [220]. A longitudinal study using 2-[18F] fluoro-2-deoxy-D-glucose PET has suggested that hippocampal reduction in glucose uptake be a predictive factor of the cognitive decline [221]. Another hypothesis suggests that the changes in the endothelium seen in AD may not directly be affected by an ischemic vascular injury but may reflect the lack of vascular remodeling occurring while the endothelium is unresponsive and overwhelmed by angiogenic stimuli [209].

Finally, the **Aß clearance hypothesis** will be discussed. Various studies have been advocating that the imbalance between clearance and production of Aß might lead to its accumulation in the wall of cerebral vessel, as well as other areas of the brains of AD patients. A variety of cell types are responsible for the production of Aß. This process takes place in the brain and in the periphery, after which Aß is carried over the BBB through receptor-mediated transcytosis [209]. A key receptor for the transportation of Aß from the blood into the brain is the one for advanced glycation endproducts (RAGE) [222]. Low-density lipoprotein receptor related protein-1 (LRP) is another, which is also classified as a major cell surface Aß clearance receptor. It is responsible for Aß clearance on VSMC [223] and the clearance of Aß in the brain across the BBB [209]. Not only a clearance of Aß as a soluble peptide from the brain interstitial fluid (ISF) can happen [224], but also a transport through chaperon proteins in the ISF, like α2-macroglobulin, apolipoprotein J, and APOE [225]. It has been suggested that the cerebral blood vessels promote the Aß drainage route along the perivascular spaces through a pulsation force [226]. Therefore, a reduction in the pulsatile flow through vessel stiffening and constriction leads to a reduced Aß clearance along the perivascular spaces with a subsequent increase in Aß deposition in the arterial wall, respectively [211,226]. The clearance into the blood stream appears to be the pathway most used, although the perivascular route has also been suggested for the clearance of Aß [227]. Furthermore, Aß may also be directly degraded by the cells of the NVU. A degradation by enzymes, like neprilysin and insulin degrading enzyme, of Aß might also take an important role in its clearance [228]. In the case of disruption of any of these pathways, which are sketched in Figure 5, an accumulation of Aß may occur and toxic Aß oligomeric and aggregated species may form and cause harmful effects on the NVU [229].

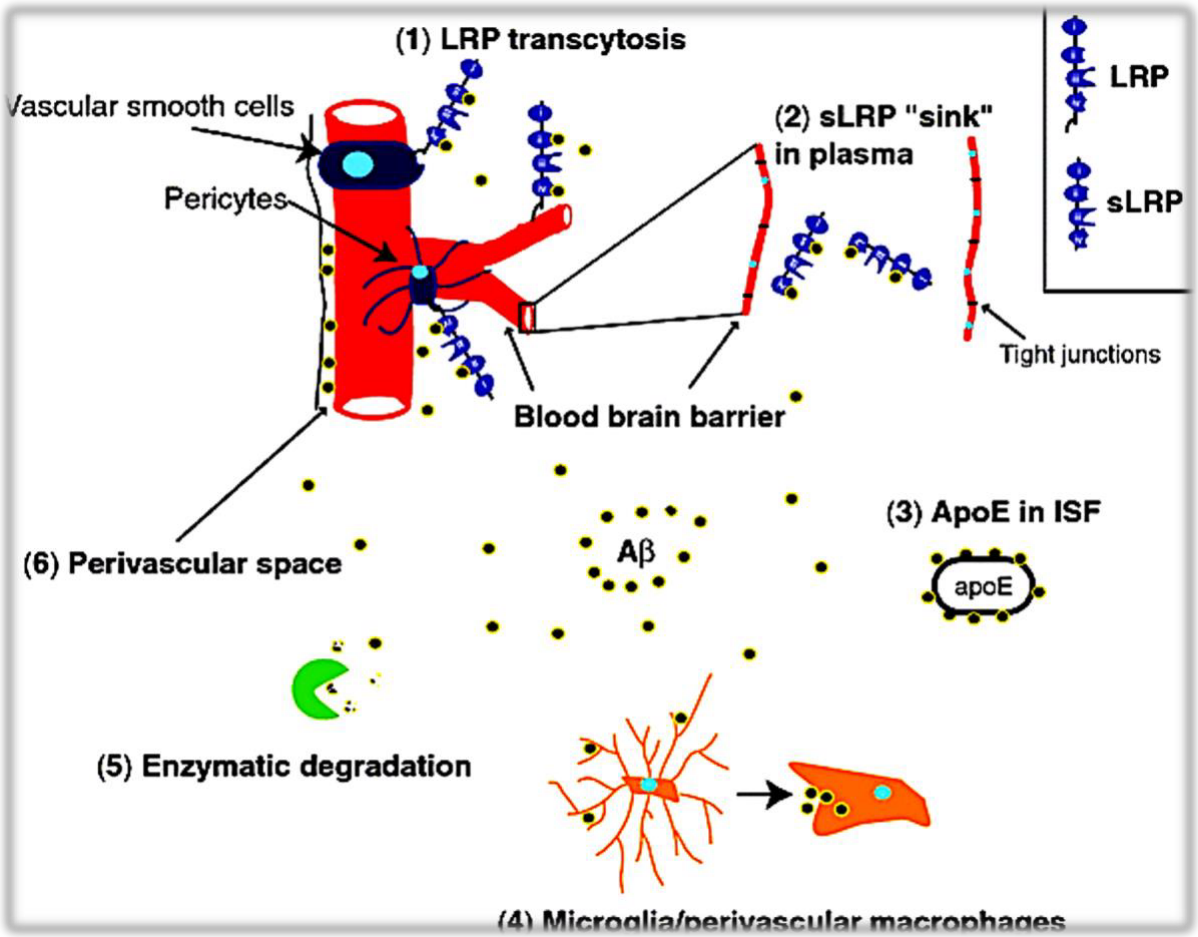

Figure 4. “Essential Aβ clearance vascular and other routes. Aβ clearance can occur via several routes: 1 LRP-mediated transcytosis (purple, receptor) across the blood–brain barrier (red, capillaries) removes Aβ from brain interstitial fluid to blood and LRP-mediated degradation of Aβ on vascular smooth muscle cells and pericytes lowers Aβ levels in perivascular spaces (blue, cells), 2 soluble LRP, sLRP-mediated (purple, soluble receptor) endogenous Aβ “sink” action in plasma increases peripheral Aβ clearance and lowers the levels of free Aβ in the circulation which in turn promotes the cell surface LRP-mediated clearance of brain-derived Aβ across the blood–brain barrier, 3 Aβ chaperones in brain interstitial fluid such as ApoE isoforms may reduce clearance of brain-derived Aβ in an isoform-specific manner, i.e., apoE4 > apoE3 or apoE2, 4 clearance of Aβ by microglia and perivascular brain macrophages (orange, cells) from brain parenchyma and perivascular spaces, respectively, 5 direct enzymatic degradation of Aβ in the brain (green, enzymes), and 6 elimination of Aβ along the perivascular spaces by passive drainage that is influenced by the arterial pulsatile flow. The illustrated pathways by all means do not cover in detail all possible routes that control Aβ levels in the brain” [209].

3.5. The Influence of Physical Exercise

The influence of physical exercise on biological processes and molecular pathways plays a pivotal role in the pathophysiological processes concerning AD and will be discussed in this chapter.

(1) Endothelial function

Regular physical activity is known to reduce risk factors that are associated with damage to endothelial function. It may even enhance endothelial function without changes in body mass index, lipid level, glucose tolerance and in blood pressure [230,231]. These improvements are suggested to arise through increased frictional forces exerted by blood flow to the endothelium as a result of moderate physical activity. This endothelial shear stress induces the production of vasodilatory substances (e.g., nitric oxide), leading to a rise in the activation and expression of endothelial nitric oxide synthase, which promotes revascularization [232]. The mobilization and abundance of endothelial progenitor cells are also associated with enhancements in vascular repair, inhibition in atherosclerosis, and stimulation in angiogenesis [232]. Note that some of these processes require mediation by nitric oxide [232]. The angiogenic response to exercise is controlled by an upregulation of the vascular endothelial growth factor (VEGF), induced through physical exercise, and maintaining the blood flow, thereby maintaining the cerebrovascular integrity and supply of nutrients and oxygen [232,233]. Furthermore, aerobic exercise induces the production of lactate, which leads to an activation of the lactate receptor hydrocarboxylic receptor 1, encouraging cerebral angiogenesis by enhancing brain VEGF levels [234]. In addition, the level of fatty acids, which do not count to the beneficial ones mentioned above, in the bloodstream can be reduced via an exercise-induced stimulation of peroxisome proliferator activated receptor-γ, promoting the storage of fatty acids in the adipose tissue [234].

(2) Immune system and inflammation

There is wide-ranging evidence for the effects of physical activity on the immune system [235]. The anti-inflammatory trajectories found may be explained by the contraction of muscles and in consequence to that producing and releasing myokines into the vascular system, especially IL-6. On the one hand, IL-6 has anti-inflammatory traits, as it enhances the expression of IL-10 and upregulates the levels of the IL-1 inhibitor, which are both anti-inflammatory. On the other, it may

diminish the expression of factors that are pro-inflammatory, such as IL-1ß and TNF-α [236,237].

Research has proposed that physical activity has a positive effect on cellular disease markers, including hyperphosphorylation of tau protein and the accumulation of Aß plaques [238,239]. An enhancement of neurotropic factors in the tissue has also been observed. These include the brain-derived neurotrophic factor (BDNF), which is acknowledged to promote a reduction in various cytokine levels, including TNF-α, and subsequently reduces neuroinflammation and eases the symptoms of AD [232].

Overall, physical activity has different effects on the immune system, depending on amount and nature. Regular moderate intensity has rather positive effects, whereas long intense sessions lead to a depression of the immune system [235,240]. Acute exercise, while promoting OS, may mediate pro-inflammatory components, however regular exercise seems to downregulate this response and enhance anti-inflammatory pathways [236].

(3) OS, neurotoxicity, and the metabolism

Various effects of physical activity on the metabolism can be observed. Low-density lipoprotein (LDL) triglyceride and cholesterol levels remain steady, whereas high-density lipoprotein (HDL) cholesterol levels are usually elevated following regular executed exercise [241]. The body is increasingly reliant on lipids as an energy substrate during endurance training, inducing systemic lipid-lowering effects, which results in skeletal muscle lipid metabolism with a subsequent rise in the oxidation of neutral lipid storge and turn-over [242]. Further, as the fatty-acid oxidation is regulated, a general decrease in lipid peroxidation through physical activity and an increase in antioxidant enzyme activity may be reached through short and long-term endurance training [232]. Still, an increase in lipid peroxidation has been shown through acute periods of high-intensity endurance training in previously untrained subjects [243]. Moreover, the muscle uptake of glucose is enhanced after acute exercise and insulin sensitivity through resistance and aerobic training [244,245].

Improved activity and clearing of Aß-degrading enzymes and an improved redox status can be observed through performing regular exercise, although acute

physical exercise typically leads to an increase in OS. Additionally, a relation between higher level in exercise and reduced levels of Aß plaques in the brain of AD patients has been observed [232,246]. Further, in a 6-month aerobic exercise intervention, a decrease by 24% compared to the control group was found in the plasma Aß1-42 levels in individuals with MCI [247]. In conclusion to various studies, a potential role of exercise can be suggested in modulating the Aß turnover [248].

(4) DNA

Extensive physical activity without incorporating the necessary amount of recovery with a repairment time of 24-27h in vivo may cause damage to the DNA, which leads to an upregulation in the generation of ROS and inflammation. Thus, a reduction in DNA repair and a downregulation in the antioxidant system is induced through this kind of exercise regime, even though the damage stands in relation to recovery periods and intensity and is only temporary [249].

As BDNF has already been mentioned previously concerning the reduction of neuroinflammation, it also possesses the ability to protect neurons through its involvement in a regulation mechanism of DNA damage repair. Therefore, an increase in the release of BDNF leads to improved repair of DNA and reduced risk of neurodegeneration [250].

(5) Intercellular communication

Physical activity promotes numerous developments in dendritic receptors and synapses, neuronal survival and even growth, synaptic plasticity, as well as neurogenesis in the hippocampal area. Additionally, it stimulates the production of neurotrophic factors, like BDNF, which endorses the modulation of dendritogenesis, synaptogenesis and neurogenesis. Exercise also increases various neurotrophins, such as the nerve growth factor as the protector of cholinergic neurons in the telencephalon, which is crucial for memory and learning [232].

When it comes to AD, the first manifestations of memory loss are interrelated with synaptic dysfunction and loss [251,252]. For low levels of BDNF, a loss of neurotrophic support can occur and is linked to reduced synaptic plasticity and neuronal survival [253]. Therefore, changes in protein homeostasis at the presynaptic level lead to

synaptic pathology and further show an association with numerous neurological disorders [252].

Further, levels of neurotransmitters, such as noradrenaline, acetylcholine, and serotonin, are elevated, and their collaboration with neurotrophins might encourage a supportive neural adaptation in the brain [232].

(6) Synaptic plasticity, cytoskeleton, and membrane proteins

Thus far, a connection between physical exercise and synaptic plasticity has been established through unclear modulations of signalling pathways [232]. Considering the aforementioned promotion of OS, modifications of cytoskeletal proteins could be induced by physical activity [254]. Furthermore, proteins associated with neuronal development and cytoskeletal function rise in levels through exercise [255]. Axonal regeneration is enhanced by the exercise-induced increments of microtubule-associated protein 2 in the hippocampus. Additionally, a specific neuronal protein (Shank) is released through the signal of BDNF/tropomyosin kinase B receptor and leads to a control of the actin cytoskeleton in dendritic spines as well as in their regression [256]. “In a preclinical rat model, moderate physical exercise was found to change the expression of synaptic proteins and cytoskeletal neurofilaments, which may trigger plasticity in regions of the brain that are related to motor function” [232].

If changes in the biological process of synaptic plasticity occur, they are assumed to contribute to numerous neurological and cognitive disorders [257,258]. Thus far, the understanding of the molecular mechanisms is poor [259]. Animal models of AD have shown that, long before the occurrence of neuronal death and amyloid plaque, the impairment of the synaptic function is an early occurrence leading to decay in memory processing [260].

(7) Cell death and apoptosis

Through physical exercise, an effect on the metabolism of substrates, such as free fatty acids and carbohydrates, as well as their mobilization, can be observed. Further, the concentration of hormones, cytokines, growth factor and the oxidative state are affected by exercise. Combined, these processes prolong cell survival and slow down cell death [261]. Thus, exercise promotes neuroprotection, neurogenesis, cell survival, as well as increased levels of neurotrophic factors.

Especially cellular AD markers stand in association with exercise, as an accumulation of Aß can be reduced [232]. “Finally, aerobic physical exercise increases the levels of telomere-stabilizing proteins, which protect against cellular senescence, and decreases the abundance of apoptotic regulators” [232].

Concerning AD, neuronal apoptosis is a crucial event besides other processes that are involved in the loss of neurons [262,263]. For example, the intrinsic apoptosis pathway is triggered through the interaction auf Aß plaques with neuronal surface cell receptors by stimulation the production of the rat sarcoma virus (RAS) and the expression of pro-apoptotic genes and the expression of caspases [262]. Through proinflammatory action, Aß also has the ability to stimulate the extrinsic apoptotic pathway, which stimulates microglia and astrocytes and in conclusion triggers the liberation of proinflammatory mediators lie TNF- α [262].

In 2023, a collaborative international guideline was published, suggesting physical activity as a primary prevention concerning dementia. Mind-body interventions support the evidence of the conversion from MCI to dementia being slowed down through physical activity. Moreover, exercise may be utilized in moderate dementia to maintain cognition [264].

3.6. Current Underlying Questions

The process of aging with all its associated positive and negative effects is influenced by a multidimensional set of variables. Living a preventive lifestyle, cognitive decline may be slowed or even prevented while aging. Thus far, specific evidence on longitudinal reciprocal relationships between those various variables is still lacking.

Intending to fill this gap of knowledge, a multicentre randomized controlled trial called the NeuroExercise study involving three European countries (Germany, Netherlands and Ireland) investigated this matter. The effects of a 12-month structured exercise program on the progression of MCI were evaluated and cognitive and physical outcomes were measured through specific tests that are explained in the paper [265].

In the following original paper, which portrays the centre piece of this work, a sub-study to the NeuroExercise study, only the German participants were included and underwent a blood drawing pre- and post the intervention period, additional to the other measurements taken. The aim was to investigate the relations of plasma levels of the robust nutritional- and antioxidant defence-related biomarkers carotenoids and tocopherols with both indicators of physical and cognitive performance in individuals with MCI following a structured exercise program.

The results of the sub-study, on which this thesis is based, can be found in the original paper in the following chapter. In the subsequent chapters, different other studies concerning the cognitive function, as well as the micronutrient status, will be discussed.

4. Results – published original work

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Influence of a 12-Month Structured Exercise Program on the Micronutrient-Cognitive Fitness-Physical Association Profiles in Mild Cognitive Impairment

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Abstract.
Background: Preventive lifestyle strategies have shown promise to slow down or prevent age-related cognitive decline. However, evidence on the reciprocal longitudinal relationships between nutrition biomarkers and cognitive and physical performance is lacking. Studying nutritional, cognitive, and physical profiles over time may help to overcome this knowledge gap.
Objective: To investigate the relationship of plasma levels of the robust nutritional- and antioxidant defense-related biomarkers carotenoids and tocopherols with both indicators of cognitive and physical performance in persons with mild cognitive impairment (MCI) participating in a structured exercise program.

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Methods: Data from 40 participants with MCI of the NeuroExercise study were analyzed. Participants had undergone a blood withdrawal for the analysis of plasma concentrations of six carotenoids, two tocopherols and retinol prior to and after one-year of structured exercise. All participants had undergone a broad spectrum of cognitive and physical performance tests.
Results: Significant associations between lipophilic micronutrients and cognitive/physical measures were observed that were previously found to play a role in cognitive and physical frailty. In particular, lutein, zeaxanthin, and lycopene are confirmed as robust, reliable, and stable indicators of nutritional defense. Importantly, these micronutrients were associated with cognitive measures prior to the physical training program and to a more prominent extent with indicators of motoric function after the physical exercise program.
Conclusion: Specific profiles of lipophilic micronutrients are associated to cognitive performance measures and, especially after a structured exercise program, to indicators of physical performance.

Keywords: Carotenoids, cognitive performance, micronutrients, mild cognitive impairment, neuropsychological tests, nutrition, physical activity

INTRODUCTION

Worldwide humanity is aging and a significant shift in the demographics is noticeable through the evolving living standards. Higher age and standards pose challenges and cognitive disorders, such as dementia, which will become an ongoing concern and major medical challenge worldwide [1]. In Italy, Japan, Wales, Germany, and the Netherlands, rising numbers of dementia cases have been observed and no disease-modifying treatment or cure for dementia has been found yet, although several attempts are ongoing and aducanumab has been formally approved as a disease-modifying treatment in the United States [2–4]. Some modifiable risk factors of dementia have already been identified in previous studies [5, 6]. Therefore, early detection of cognitive decline has become increasingly important to establish treatment approaches or lifestyle modifications as early as possible. Early stages of particular interest are age-related cognitive decline, subjective cognitive impairment (SCI), and mild cognitive impairment (MCI) due to an increased risk of the individual developing dementia [7, 8].

Among modifiable risk factors, physical inactivity shows the highest population-attributable risk (PAR) of Alzheimer's disease (AD): USA (21.0%, 95% CI 5.8–36.6), Europe (20.3%, 5.6–35.6), and the UK (21.8%, 6.1–37.7) [9]. Previous studies have shown that 6 to 12 months of exercise can maintain or improve cognition among patients with dementia or MCI [10]. Additionally, interventions focusing on physical activity, cognitive training, overall lifestyle changes, and dietary interventions receive greater attention. After two decades of research, strong evidence is available on dementia-preventive effects of B vitamins, vitamin E, and n-3 fatty acids [11], which stresses the importance of analyzing physical functions as well as a nutritional status to establish multidimensional concepts as treatment approaches [5, 12].

Oxidative stress has frequently been described as a possible pathophysiological mechanism responsible for the development of cognitive impairment [13]. As oxidative stress is not only influenced by physical activity [14], but also substantially by nutrition, it may explain the importance of multimodal/holistic lifestyle changes [15]. Oxidative stress can be measured through several biomarkers, which play a role in the defense mechanism against free radicals [16]. Previous results have shown an association between nutrition- and antioxidant defense-related biomarkers in participants with MCI in the NeuroExercise Study in Germany [17]. However, the influence of a one-year training intervention on the aforementioned biomarkers and their influence on cognitive and physical function post-intervention has not been investigated yet. Therefore, this work aimed to determine the reciprocal relationships between nutrition biomarkers, cognitive performance, and physical performance in persons with MCI that underwent a structured exercise program for one year [6].

METHODS

Participants

Across three European countries, a randomized controlled trial—the NeuroExercise Study—investigated the effects of exercise therapy on the progression of MCI [18, 19]. For the purpose of the present sub-study, the participants

were recruited in Germany at the German Sport University (GSU). The study was conducted in accordance with the declaration of Helsinki (1975) and approved by the research ethics committee of the GSU. The participants were recruited through newspaper advertisements as well as editorials. Participants provided informed written consent to the study procedures [17, 20]. Inclusion criteria was a score between 18 and 26 on the Montreal Cognitive Assessment (MoCA), which is a widely known and validated assessment tool with the score above reflecting MCI [21]; pretesting distinguished between amnestic and non-amnestic MCI, where educational cut-offs were applied: –2 Standard Deviation (SD) for low education (<10 years of education), –1.5 SD for the middle group (10–13 years of education), and –1 SD for the highly educated (>13 years of education). These were taken from the delayed recall portion of the age-adjusted delayed memory index of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Score of <85) as previously described [17, 18, 20, 22]. The exclusion criteria included a diagnosis of AD or any other dementia, as well as a family history of early-onset dementia; epileptic seizures in the past two years; participation in any investigational drug study, significant history of alcoholism or drug abuse within last 10 years and history of vitamin B12 deficiency or hypothyroidism [17, 18]. A complete list of in- and exclusion criteria has been published elsewhere [23].

After being deemed eligible for the study, participants underwent a baseline assessment, which included the collection of various data such as their lifestyle habits, different neuropsychological testing as well as general physical and cardiovascular testing. Afterwards, participants were randomly stratified into three different groups using a centrally controlled computer-generated randomization list: Stretching and Toning (S&T) or Aerobic Exercise (AE), which underwent 3 × 45 min exercise sessions per week over a time period of 12 months, or a non-exercising Control Group (CG) following standard care [18, 20]. Exercise intensity was monitored using Borg's Rating of Perceived Exertion (RPE). An RPE of at least 13 was the aim of the AE group, whereas the S&T group had a target RPE <10 [24, 25].

Study overview

Data assessment occurred before (T0) and after 12 months of exercise intervention (T12). Besides a neuropsychological test battery, quality of life measures, and a physical fitness evaluation [20], a blood drawing was also completed [6, 17, 20]. At baseline (T0), blood drawing was completed before randomizing participants into the different groups.

Cognitive function assessment

The MoCA, which has also been validated to detect MCI with high sensitivity and specificity [17, 21], was used to acquire a broad measure of cognitive function. For evaluating the speed of processing and executive functions, the Trail Making Test A and B (TMT A and B) were used [26]. These two tests were completed as a paper-and-pencil-based task [26, 27]. Letter fluency and category fluency were used to test verbal functioning [28, 29]. Moreover, the CogState Battery, which is a computer-based neuropsychological test battery, was applied. It consisted of the following tasks: Detection Task, Identification Task, One Card Learning Task (OCL), One Back Task (OBT), International Shopping List Task (ISLT), International Shopping List Recall Task (ISLT Recall) [17, 18, 30].

Physical activity assessment

Cardiorespiratory fitness was assessed using an incremental exercise test on a cycle ergometer. Estimated $\dot{V}O_2$peak (mL/kg/min), which was defined as outcome measure for cardiorespiratory fitness, was used as an outcome. The health-related quality of life for people with Dementia (DemQOL) was used to evaluate the health-related quality of life and the Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire (LAPAQ) to assess physical activity in the preceding 14 days [31, 32].

Mean number of steps per day was assessed through wearing an activity watch, which was asked to be worn on the non-dominant arm for a whole week for 24 h a day [20, 33]. The Timed Up and Go test (TUG), which displays a person's ability to go out on their own [34], as well as the 30 Seconds Chair Stand Test (CST) [35] as a proxy for endurance and lower limb strength were assessed. Bilateral Hand grip strength (left-HGL; right-HGR) was evaluated through a Jamar Digital Dynamometer, which has been shown to correlate significantly with upper limb strength [18]. The physical activity assessments have been described in detail elsewhere [6, 18].

Table 1
Group demographics

	S&T ($n = 14$)	AE ($n = 12$)	CG (N = 14)	p
Age (y)	78.9 ± 3.8	77.2 ± 4.4	76.8 ± 6.4	0.522
Sex (female)	8 (57.1%)	5 (41.7%)	5 (35.7%)	0,503
BMI	25.3 ± 2.8	25.6 ± 2.2	26.5 ± 3.9	0.556
Education, N (%)				(χ^2) 0.018
Low	1 (7.15%)	0 (0.0%)	1 (7.2%)	
Middle	12 (85.7%)	4 (33.3%)	10 (71.4%)	
High	1 (7.15%)	8 (66.6%)	3 (21.4%)	
No. of medication used	1.86 ± 1.06	1.50 ± 1.94	1.50 ± 1.35	(χ^2) 0.234
RBANS	83.07 ± 12.86	78.75 ± 13.85	78.77 ± 13.81	0.636
Moca T0 (Score 0/30)	23.4 ± 1,28	23.08 ± 2.64	22.43 ± 2.17	0.442

S&T, stretching and toning group; AE, aerobic exercise group; CG, control group; BMI, body mass index; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; MoCA, Montreal Cognitive Assessment.

Lipophilic antioxidant micronutrients

The lipophilic antioxidant micronutrients were measured after blood drawing in a heparinized tube, which was centrifuged immediately, plasma separated and stored frozen at –80°C until analysis. Through High Performance Liquid Chromatography (HPLC) with UV-vis detection at 450 nm, the different carotenoids—lutein, zeaxanthin, β-cryptoxanthin, lycopene, and α-and β-carotene—were analyzed according to Stahl et al. [36, 37]. To detect the quantitation of retinol (vitamin A) and α- and γ-tocopherol (vitamin E), a second UV-vis detector was set at 325 and 292 nm and connected in series. For each micronutrient, the recovery from the column accounted for 90%. For all carotenoids, the calibration curves appeared linear from 0 to 1000 nmol/L with a correlation coefficient of 0.99. The coefficient of variation of the intra- and inter-assay precision was between 5 and 15% [17].

Subgroup analysis

For this subgroup analysis, 40 complete datasets (pre and post-test) were obtained. The smaller sample size compared to the main study was due to missing data [6], particularly on lipophilic antioxidant micronutrients. As participation in micronutrient assessment was voluntary and not part of the original proposal of the NeuroExercise project, some participants decided against the additional blood drawing.

Statistical analysis

IBM SPSS Statistics 26[ã] was utilized to analyze the data with α set at 0.05. After verifying normality using Shapiro Wilk, a repeated measures of variance analysis (ANOVA) was carried out with the within-subjects factor time (pre- and post-test) and the between-subjects factor group (S&T, AE, CG). Variables pertaining of cognitive function (CogState Battery, MoCA, TMT A+B, verbal fluency), physical fitness assessment (VO2peak, Grip Strength, LAPAQ, Steps per day, TUG, CST), quality of life (DemQOL) and lipophilic antioxidant micronutrients (lutein, zeaxanthin, cryptoxanthin, lycopene, α-carotene, β-carotene, α-tocopherol, γ-tocopherol, retinol) were compared using the aforementioned analysis. In case of significant interaction effects of time*group Bonferroni corrected *post-hoc* pairwise comparisons were conducted.

Furthermore, Pearson's correlation was used to assess correlations between lipophilic antioxidant micronutrients and the other aforementioned parameters at post-tests [17].

One way ANOVA analyses were used to test differences in demographics between the three groups. Data are presented as means ± standard deviation.

RESULTS

Baseline demographics, as well as physical and neuropsychological characteristics, are displayed in Table 1. Education years differed significantly between the groups, as higher educated participants were in the AE group ($p = 0.018$). No further differences were found at baseline. The laboratory values of the lipophilic micronutrients, as well as the physical and cognitive data, can be found in the supplementary materials (Supplementary Table 1).

Table 2
Significant correlations between lipophilic micronutrients and physical measures after the one-year

Correlation	Group	*r*	*p*
Quality of life measurement: Lutein/ DemQOL	CG	0.716	0.004
Lutein/ Steps per day	AE	0.747	0.013
Lutein/ CST	S&T	0.727	0.003
Lutein/ CST	EG	0.424	0.044
Lutein/ HGL	EG	–0.406	0.049
Zeaxanthin/ LAPAQ	S&T	–0.555	0.039
Zeaxanthin/ LAPAQ	EG	–0.464	0.026
Zeaxanthin/ CST	S&T	0.766	0.001
Zeaxanthin/ CST	EG	0.418	0.047
Zeaxanthin/ HGR	EG	–0.417	0.043
Zeaxanthin/ HGL	EG	–0.427	0.038
β-Cryptoxanthin/ HGR	EG	–0.405	0.050
β-Cryptoxanthin/ HGL	S&T	–0.560	0.037
β-Cryptoxanthin/ HGL	EG	–0.459	0.024
Lycopene/ VO2peak	EG	0.421	0.036
Lycopene/ DemQOL	AE	–0.624	0.040
Lycopene/ DemQOL	EG	–0.412	0.041
Lycopene/ CST	EG	0.428	0.041
α-Carotene/ DemQOL	CG	0.671	0.009
β-Carotene/ DemQOL	AE	–0.605	0.049
β-Carotene/ DemQOL	CG	0.585	0.028
β-Carotene/ CST	S&T	0.667	0.009
α-Tocopherol/ HGL	EG	–0.423	0.040

S&T, stretching and toning group; AE, aerobic exercise group; CG, control group; EG, exercise group; DemQOL, health-related quality of life for people with Dementia; LAPAQ, Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire; CST, 30 Seconds Chair Stand; HGR, Hand Grip Strength Right; HGL, Hand Grip Strength Left.

Repeated measures ANOVA

Repeated measures ANOVA revealed a significant interaction effect for time*group for the variables $\dot{V}O_2$peak ($F_{2,36} = 7.641$; $p = 0.002$) and DemQOL ($F_{2,36} = 6.505$; $p = 0.004$). *Post-hoc* pairwise comparisons showed that both the AE ($p = 0.317$) and S&T ($p = 0.061$) tended to increase in $\dot{V}O_2$peak between pre and post-test, whereas a significant decrease in fitness was observed for the CG ($p = 0.002$). The S&T further improved their quality of life significantly ($p < 0.001$), whereas this was not found for AE ($p = 0.936$) and CG ($p = 0.539$) after applying Bonferroni corrected *post-hoc* tests. Apart from $\dot{V}O_2$peak and quality of life, repeated measures ANOVA did not reveal further significant changes.

Lipophilic micronutrients and functional abilities

As displayed in Table 2, several significant associations were found between the micronutrients measured and the indicators of functional abilities after one-year of exercise. Interestingly, no association was found between the CG's micronutrients level and the functional abilities. In the cumulative analysis of participants undergoing the NeuroExercise training program (S&T+AE), which are described as the Exercise Group (EG), significant associations were found between physical performance readouts and lutein with CST (EG) ($p = 0.044$) and HGL (EG) ($p = 0.049$), zeaxanthin and LAPAQ (EG) ($p = 0.026$), as well as with CST (EG) ($p = 0.047$), HGR (EG) ($p = 0.043$) and HGL (EG) ($p = 0.038$); between β-cryptoxanthin and HGR (EG) ($p = 0.050$) and HGL (EG) ($p = 0.024$), lycopene and CST (EG) ($p = 0.041$) and α-tocopherol and HGL (EG) ($p = 0.040$) (Table 2).

Lipophilic micronutrients and its associations with cognitive performance and quality of life

Cognitive performance measures were significantly associated with lycopene and CogState Detection (EG) ($p = 0.044$) as well as with CogState Identification (EG) ($p = 0.004$). In the CG sporadic associations between α-carotene and β-carotene and DemQOL were observed (Table 2), as well as

Table 3
Significant correlations between lipophilic micronutrients and cognitive measures after the one-year intervention

Correlation	Group	*r*	*p*
Zeaxanthin/ CogState Detection	CG	–0.553	0.040
Lycopene/ Cogstate Detection	AE	–0.744	0.006
Lycopene/ Cogstate Detection	EG	–0.398	0.044
Lycopene/ Cogstate Identification	AE	–0.764	0.004
Lycopene/ Cogstate Identification	EG	–0.551	0.004
α-Carotene/OCL	CG	0.565	0.035
β-Carotene/OCL	AE	0.608	0.036
β-Carotene/OCL	CG	0.536	0.048

S&T, stretching and toning group; AE, aerobic exercise group; CG, control group; EG, exercise group; OCL, One Card Learning Task.

between zeaxanthin and CogState Detection and both α-carotene and β-carotene with OCL.

DISCUSSION

As previously shown by Gerger et al., this substudy to the NeuroExercise multi controlled study also revealed that there is a significant association between plasma levels of various lipophilic antioxidant micronutrients with both physical and cognitive performance [6, 17]. While one year of controlled exercise did not lead to significant changes in the concentrations in the individual plasma levels of the various lipophilic micronutrients, one important observation could be made at follow-up: In relationship to cognitive and motoric functions, the micronutrients were shown to associate with cognitive measures prior to the physical training program and with indicators of motoric function after the one-year physical exercise program [17]. This is in agreement with research showing that physical exercise contributes to the antioxidant defense mechanism of the body [38]. This shift in the association of micronutrients becoming predominantly indicators of physical fitness after one-year of structured exercise supports the use of robust lipophilic micronutrients as a monitoring instrument for the effect of lifestyle strategies [39]. Exercise is enforcing various stressors to the human body and, thus, increasing exposure to reactive nitrogen species (RNS) and reactive oxygen species (ROS). Oxidative balance is preserved through a multifaceted antioxidant defense system of antioxidant enzymes within the physiological bounds to decrease the chances for oxidative damage [40]. RNS and ROS function as messengers through redox-sensitive protein interaction to regulate various processes in the body such as mitochondrial biogenesis or immune response [41]. Further, exercise upregulates the endogenous antioxidant defense system [42].

The numbers of studies investigating the various associations between physical and cognitive performance with antioxidative defense systems are small but increasing [17, 38]. In order to further explore the impact nutrition has on cognitive brain function and brain health, the interdisciplinary field of 'Nutritional Cognitive Neuroscience' has recently been introduced and has already contributed to this new research area with their pathophysiological investigations and nutritional intervention studies. Especially the field of cognitive, physical, and dietary interventions has recently garnered attention in the scientific community, with our study adding to the existing body of knowledge. The focus of that attention has been on their success in showing that different stages of cognitive impairment can be influenced by physical activity and nutrition. Here, oxidative stress was defined as the influencing factor of attention [5]. Moreover, previous evidence elaborated that in age-related cognitive neurodegeneration, oxidative distress and eustress play a major role [5, 16, 43–45]. 'Oxidative distress' describes adverse elevated levels of ROS. These elevated levels, especially in combination with changes in O_2 levels, may result in molecular damage to the central nervous system due to its relative sensitivity [5, 43]. The carotenoids analyzed in the present investigation are shown to be efficient lipophilic antioxidants in the living being [46]. They function as robust biomarkers of dietary exposure occurring in different organisms, i.e., animals, plants, and microorganisms. However, it should always be considered that different variables, such as carotenoid distribution, metabolism, and bioavailability, as well as the dietary supply, depend on various host factors, including genetic makeup, age,

sex, lifestyle, and diseases [47]. As the NeuroExercise study aimed to change lifestyle habits by increasing physical activity but did not control for further host factors, this may explain the lack of statistically relevant changes in our substudy. Similar to the variation concerning the host factors, there is also a different distribution of the carotenoids in various organs in the body. Curiously, in the frontal and occipital lobes of the human brain tissue, xanthophylls account for 66–77% of the total carotenoids [48].

Another important influential construct on oxidative stress should be considered, as ROS and similar components are not only generated internally, but also influenced by external factors. The most obvious influence in daily life is air pollution with its gases, metals, organic compounds, and a diverse mixture of particulate matter [49, 50]. It is commonly known that air pollution distresses the state of health through promoting respiratory as well as cardiovascular morbidity and mortality with recent research suggesting that these effects even go as far as affecting the brain [51, 52]. Metal toxicity is a further factor, as heavy metals are generating ROS, which in consequence might lead to toxic mechanisms, like hepatotoxicity, neurotoxicity, and nephrotoxicity [53, 54]. As the stratospheric ozone is depleting, ultraviolet (UV) radiation may present another concern. Through UVA, as well as UVB radiation, research suggests an effect in adverse biological mechanisms, such as DNA and membrane damage, leading to phototoxicity, inflammation, skin aging, and malignant tumors [50]. Inflammatory pathways are also activated through an alteration in enzymes induced by pesticides affecting multiple organs [50]. As all participants in this sub-study lived in urban area of Cologne, their exposure to environmental factors was similar. Unhealthy lifestyle habits such as alcohol abuse and cigarette smoke are also defined as environmental factors [50]. However, alcohol abuse was included as an exclusion criterion of the NeuroExercise, and, thus, did most probably not affect results of our sub-study. Future research, especially with participants from different areas (i.e., urban, rural), need to take these factors into account.

In the Healthy Aging in Neighborhoods of Diversity across the Life Span study, statistical significance was found between vitamin E and verbal memory performance ($p = 0.002$), with this association largely driven by the carotenoid lycopene [55]. Another inverse association was assessed between lutein-zeaxanthin and lycopene with brain global pathology [56]. This can be observed in previous work of Polidori et al. and Dias et al., who have shown that lycopene, zeaxanthin, and lutein had a significantly lower concentration in patients with Alzheimer's disease that suffered from vascular comorbidities than in healthy subjects [57, 58]. In the present study, a significant correlation was found between the carotenoid lycopene and the CogState Detection and the CogState Identification in the Aerobic Exercise Group, as well as in the general Exercise Group. Both tests belong to the CogState Battery, with the Detection Task assessing psychomotor function and the Identification Task evaluating the attention of the individual [30]. A significant correlation between cognitive measures and endothelial function [59, 60], as well as between cognitive measures and micronutrients is well-established [5, 13, 16, 17, 48, 57, 58]. The collected data did not support this notion, as no changes in cognition were found. Nevertheless, positive correlations between both lutein and zeaxanthin levels in subjects within the S&T group and the EG and their ability to perform in the chair stand test were found. Furthermore, performance success was positively correlated with lycopene in the EG and β-carotene in the S&T group. Lutein and its isomer, zeaxanthin, accumulate in the human brain over time. They form a macular pigment by crossing the blood-retina barrier to serve as a protection against age-related eye diseases. Other studies have also observed an association between cognitive functions and optical density of the macular pigment indicating the presence of lutein and zeaxanthin in the central retina. The difference in observations may be explained by differences in methods. Where Stringham et al. observed physiological factors in the retina, which, unlike blood serum, have not been shown to at least weakly reflect lutein and zeaxanthin concentration in the central nervous system [61]. The lack of significant changes in lipophilic antioxidant micronutrients over the course of the study is potentially due to the lack of nutritional intervention in the NeuroExercise Study.

It needs mentioning that other nutritional components may also impact cognitive function. A high intake of saturated fatty acids can enhance cognitive impairment, whereas a high consumption of the omega-3 group might reduce the risk of dementia [62, 63]. In addition, curcumin may have positive effects in individuals with MCI; however, no significant differences were established for individuals affected by AD either supplementing curcumin or a placebo [64]. Nevertheless, another study revealed positive effects

on chronic inflammatory processes influencing Aβ protein plaques in the brain [65]. Therefore, supplementing curcumin may present a promising treatment approach that could be implanted in multi-domain type interventions (e.g., exercise and nutritional).

Taking around 500 mg of caffeine might also have therapeutic effects when it comes to neuromodulatory and neuroprotective properties, as Aβ levels in the brain decreased in animal studies through the inhibition of synthesizing enzymes [66]. Additionally, a resveratrol intake improved different measures of cognitive performance [67], but has similarly led to negative side effects such as hyperplastic changes of kidneys and gallbladder, diarrhea, vomiting, leukocytosis, and more. A lower dose of 0.3 g/kg b.w./day for 4 weeks did not show any side effects [68, 69] and may be added to multi-domain interventions. Similarly, probiotic bacteria should be taken into account when thinking about such studies, as these contain anti-inflammatory effects on the digestive system with various benefits. They prevent pro-inflammatory components of infiltrating the bloodstream, which are possibly involved in neurological diseases [70, 71], and in the case of a dysbiosis may even get through the brain blood barrier and affect the pathogenesis of AD [72, 73]. Taken together with results from our sub-study, multidimensional treatment approaches are warranted in future studies, which assess holistic lifestyle changes that include both exercise as well as nutritional interventions.

The present study has some limitations, especially the small sample size that restricts the generalizability of the data. It is also important to note that we observed differences in educational levels between the groups at baseline but did not include these in the analysis. As the groups were randomly stratified using an independent statistician's computer-generated list, these differences occurred rather by chance. Furthermore, only two participants of the total sample had a low educational status with less than 10 years. As very low to none education is mainly known to affect dietary patterns, the difference between individuals with 10–13 years of education and those with over 13 years may be insignificant. However, the role of education needs to be further clarified in future studies using bigger sample sizes. Even though our sample size was rather small, the values observed in our study are in accordance with previous research. Furthermore, the unique study design with an exercise intervention over 12 months, as well as the extensive yet standardized data collection with robust biomarkers, and data regarding physical and cognitive performance, allows comparability to previous and future studies. The nutritional and dietary status were not controlled within this sub-study at follow-up, which may have influenced micronutrient status. However, participants stated to have not substantially changed their lifestyle behavior other than exercise. As this was similar between the control and intervention groups, we believe that dietary patterns, which were similar at baseline [17], did not differ between the various groups. Nevertheless, data needs to be interpreted cautiously given this limitation and future studies are warranted to assess and control for nutritional changes. As nutrition was not a major focus of the NeuroExercise study, this may further explain the lack of changes observed over the course of the study. Whereas physical performance increased, micronutrient profile and cognitive function did not change. However, the associations between lifestyle factors and cognition observed in the study demonstrate the importance of assessing the cause and effect of multidimensional treatment approaches, including exercise and nutrition, on cognition.

Conclusions

In this subsample of 40 participants of the NeuroExercise study, cognition and micronutrient levels did not differ between the intervention groups and the control group after 12 months of an exercise program, even though differences in fitness were observed between the groups. Nevertheless, significant correlations between the plasma levels of carotenoids and several cognitive and physical data indicate an association between these parameters. As lifestyle factors such as physical activity and nutritional habits have gained attention in regard to disease prevention, the detected associations may point towards multifactorial lifestyle changes. Combined nutritional and physical interventions may have bigger effects on cognition in persons at risk for dementia. Therefore, further studies are warranted that investigate the role of dietary intake and its influence on the plasma carotenoid levels as well as the effect on cognitive and physical performance. Therefore, multidimensional approaches should be established to deepen not only our understanding of the complex processes of the aging brain but also provide insight into potential treatment approaches. With humanity ageing worldwide and with a significant shift in the demographics, such treatment approaches would be of utter importance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. The funders (EU JPND) had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

SUPPLEMENTARY MATERIAL

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Supplementary Material

Influence of a 12-Month Structured Exercise Program on the Micronutrient-Cognitive Fitness-Physical Association Profiles in Mild Cognitive Impairment

Supplementary Table 1. Means and standard deviation of the data obtained at T0 and T2

	S&T (N=14)						AE (N=12)						CG (N=14)						Time* Group
	T0			T2			T0			T2			T0			T2			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	p
MoCA (score 0/30)	14	23.43	1.28	14	25.64	2.17	12	23.08	2.64	11	24.00	4.38	14	22.43	2.17	14	24.00	1.80	0.486
TMT_A (s)	14	43.97	12.56	14	43.47	19.29	12	50.59	21.16	12	48.53	18.82	14	51.02	25.70	14	49.52	23.56	0.971
TMT_B (s)	14	106.18	28.36	14	116.82	55.11	12	166.17	86.61	12	138.54	82.98	14	159.44	73.17	14	137.73	69.79	0.190
Delis1 (number of words/min)	14	11.79	3.38	14	12.31	3.49	12	13.20	4.57	12	13.34	4.92	14	11.29	3.44	14	11.29	3.44	0.795
Delis2 (number of words/min)	14	18.57	3.92	14	19.93	5.43	12	18.75	5.53	12	18.00	7.34	13	16.23	3.37	14	16.64	5.12	0.484
VO2peak (mL/kg/min)	14	22.53	4.25	14	23.37	3.07	12	24.48	6.54	11	25.91	7.82	14	23.74	4.60	14	21.05	3.74	0.002
DEMQOL (total score)	14	91.36	8.62	14	90.86	10.60	12	83.67	16.00	11	97.64	11.16	14	88.79	11.26	14	87.07	15.52	0.004
LAPAQ (min)	14	251.07	149.42	14	310.71	187.77	12	263.75	177.20	9	296.67	96.86	14	176.79	120.59	14	211.21	139.16	0.915
Steps/day	13	10880.13	4490.79	13	9961.02	2577.88	10	11639.54	4090.32	10	9959.71	4255.41	13	8616.99	2614.87	9	9381.88	4181.04	0.356
TUG (s)	14	8.64	1.04	14	8.57	1.12	11	9.06	2.04	10	8.73	1.17	14	9.09	1.56	14	9.06	1.56	0.992
CST (total number of stands within 30 s)	14	13.86	2.32	14	14.36	3.37	11	12.82	3.60	9	16.33	5.32	14	12.57	3.48	14	12.79	3.21	0.285
GripStrength_R (kg)	14	28.40	8.16	14	26.52	8.06	11	35.19	10.42	10	30.53	8.84	14	33.57	11.04	13	34.54	9.87	0.480
GripStrenght_L (kg)	14	25.96	6.69	14	25.26	8.19	11	33.45	10.14	10	28.55	10.20	14	30.97	9.41	13	32.70	9.89	0.301
CogState_DET (ms log10)	14	2.62	0.08	14	2.65	0.08	12	2.64	0.10	12	2.64	0.10	14	2.64	0.10	14	2.64	0.08	0.443

CogState_IDN (ms log10)	14	2.80	0.06	14	2.81	0.07	12	2.81	0.08	12	2.79	0.052	14	2.78	0.12	14	2.80	0.06	0.216
CogState_OCL (number of correct inputs)	14	0.99	0.06	14	0.99	0.10	12	0.93	0.11	12	0.94	0.10	14	0.91	0.09	14	0.94	0.09	0.713
CogState_ONB (number of correct inputs)	14	1.28	0.14	14	1.37	0.13	12	1.22	0.19	12	1.19	0.19	14	1.30	0.16	14	1.29	0.15	0.254
CogState_ISLT (number of recalled items)	14	21.71	4.83	14	20.71	4.83	12	19.25	3.72	12	21.58	7.45	14	19.22	3.38	13	20.46	3.57	0.254
CogState_ISLT_RE (number of recalled items)	14	6.00	2.63	14	6.21	2.26	12	4.92	2.88	12	6.17	3.83	14	5.00	2.25	13	5.54	2.11	0.584
Lutein (µM)	14	0.59	0.40	14	0.42	0.20	12	0.42	0.18	12	0.32	0.11	14	0.40	0.16	14	0.30	0.14	0.462
Zeaxanthin (µM)	14	0.15	0.19	14	0.07	0.05	12	0.08	0.04	12	0.05	0.01	14	0.08	0.03	14	0.05	0.02	0.335
Cryptoxanthin (µM)	14	0.54	0.33	14	0.34	0.25	12	0.41	0.34	12	0.25	0.17	14	0.45	0.57	14	0.28	0.30	0.906
Lycopene (µM)	14	0.50	0.18	14	0.39	0.15	12	0.61	0.35	12	0.38	0.13	14	0.57	0.26	14	0.41	0.18	0.282
Alpha_Carotene (µM)	14	0.16	0.10	14	0.10	0.08	12	0.10	0.04	12	0.08	0.04	14	0.13	0.08	14	0.10	0.05	0.108
Beta_Carotene (µM)	14	1.03	0.90	14	0.67	0.51	12	0.57	0.31	12	0.40	0.23	14	0.69	0.38	14	0.49	0.23	0.278
Alpha_Tocopherol (µM)	14	29.95	9.51	14	28.82	3.82	12	27.31	5.29	12	27.30	7.40	14	26.90	5.53	14	26.92	6.59	0.865
Gamma_Tocopherol (µM)	0						12	2.17	1.02	0			14	2.14	0.53	0			
Retinol (µM)	14	1.62	0.44	2	1.69	0.80	12	1.39	0.33	1	1.23		14	1.43	0.27	1	0.72		0.867

S&T, stretching and toning group; AE, aerobic exercise group; CG, control group; BMI, body mass index; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; MoCA, Montreal Cognitive Assessment; TMT A, Trail Making Test A; TMT B, Trail Making Test B; Delis 1, Letter Fluency; Delis 2= Category Fluency; VO2PEAK, VO2PEAK; DemQOL, health-related quality of life for people with Dementia; LAPAQ, Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire; Steps, steps per day; TUG, Timed Up and Go; CST, 30 Seconds Chair Stand; HGR, Hand Grip Strength Right; HGL, Hand Grip Strength Left; OCL, One Card Learning Task; OBT, One Back Task; ISLT, International Shopping List Task; ISLT Recall, International Shopping List Recall Task

5. Discussion

5.1. Key findings and Limitations – a Continuation of Previous Discussion

As this study is a sub-study to the NeuroExercise study, similar results to the original study but also some differences can be found. In the primary complete analysis of the Neuroexercise study, no changes could be observed in the 12-month exercise intervention concerning cognitive performance in individuals with amnestic MCI in comparison to a non-exercise CG [265]. However, effects on the physical performance could be observed after the 12-month exercise intervention, which possibly can be assumed as an important moderator for the progression of long term disease and demands a further follow-up investigation in the long-term [265].

The sub-study investigated the associations between cognitive and physical variables and micronutrient status. Significant associations between plasma levels of lipophilic antioxidant micronutrients and cognitive and physical performance were found [266]. Data previously presented by Gerger et al. found that micronutrients mainly correlated with cognitive measures prior to the physical intervention [1]. By contrast, the main associations in the post-intervention data were observed between micronutrient status and physical fitness variables, which aligns with previous research findings [1,267]. It is hypothesized that these associations, with special focus on the ones concerning micronutrient status, might partly indicate physical fitness trajectories following a one-year physical intervention. Therefore, it might be possible to use those micronutrients to monitor lifestyle strategies, as physical exercise seems to contribute to the antioxidant defence mechanism [268,269].

Another point to consider is that MCI is described as a multicausal syndrome, rather than having a single cause [270,271]. Consideration of various variables is crucial when looking at the micronutrient behavior, such as dietary supply, metabolism, distribution and bioavailability, all of which are influenced by age, sex, diseases, lifestyle and genetic makeup [272]. Therefore, prescription of a single intervention will unlikely present as a suitable treatment for the majority of the MCI population considering the multidimensional pathophysiology of the condition. As a multidimensional approach would seem to be the gold standard, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) investigated the effects of a 2-year multidomain-type intervention, including exercise, diet and cognitive training in a double-blind randomized controlled trail. A total of 1260 individuals between the age of 60 and 77 years were randomly assigned to the intervention group (n=631) and the control group (n=629). Positive results were observed on global cognitive function, executive function, and

processing speed in people at risk for cognitive decline who did not have a measurable cognitive impairment [273].

A small number of studies have attempted to establish the broad spectrum of these robust biomarkers of antioxidant defence and nutrition, and to consider both cognitive and physical performance of patients. To assess an association between specific micronutrients and selected cognitive domains, various cognitive tests were used, such as the neuropsychological battery, a validated and gamified computerized test (CogState).

While the main study had a relatively large sample size, the low participant number in this sub-study counts as a limitation. Nonetheless, the results of the sub-study align with most of the data mentioned in earlier chapters of this thesis and with data reported by other literature. There were also differences in educational level, which were not included in the analysis, and rather occurred by chance as the groups were stratified randomly through a computerized list. In the follow-up within the sub-study, the dietary and nutritional status was not recorded, with the participants in each group stating not to have changed their dietary routines during the intervention. Thus, interpretation needs to be made cautiously and the nutritional intake should be documented in further studies for better data interpretation.

Moreover, the interpretability of the results of the sub-study is increased through a strict selection of MCI aiding accurate inclusion and exclusion criteria, the long period of intervention, the very comprehensive neuropsychological battery, and an overall multi-centre design. An overall score of the cognitive function, which was set as the primary outcome, was established through the combination of the different cognitive tests, as well as for the various subdomain of cognitive function, to stipulate a more reliable and valid psychometrically concept [265]. Regarding the role of carotenoids in cognitive function, this study found correlation, which does of course not imply causation.

5.2. The Effects of Cognitive Training – BrainProtect®

The effect of cognitive training concerning dementia management is being explored through research, for example through the BrainProtect® study [274]. Although the WHO guideline "Reducing Dementia Risk" from 2019 advocated the pursuit of physical activity, cognitive training, a balanced diet and social interaction have been shown to endorse effective prevention [275].

Despite the development of various lifestyle programs incorporating cognitive training, a debate is still ongoing concerning the most effective strategy to preserve cognitive health. The German Association for Memory Training (Bundesverband Gedächtnistraining e.V.) developed the BrainProtect® cognitive training program and studied its effect. With the additional inclusion of physical exercise and nutrition counseling involving social interaction, the 289 cognitively healthy participants underwent a 90-minute session of cognitive exercise for eight weeks. An improvement in cognitive scores could be observed after the intervention in up to 80% of the participants and a rise in all cognitive domains explored could be found. Even though significance for verbal fluency ($p=0.021$), visual memory ($p=0.013$), visuo-constructive functions ($p=0.034$), and health-related quality of life ($p=0.009$) was lost after adjustment, it can be assumed that several changes were clinically relevant. These results lead to the assumption that BrainProtect® might improve mental fitness through the cognition-centred training already after 8 weeks. However, further research is needed to confirm these results [274].

5.3. ZNAge – a biobanking study

At the same time as the projects mentioned above, a randomized controlled study by our research team called "Jede Jeck is anders: Ergänzendes geriatrisches Management älterer Patienten in der Notaufnahme" (Diversity: Complementary Geriatric Management of Older Patients in the Emergency Unit) was conducted. The study investigates whether an early risk evaluation in older patients with suggestions concerning the ongoing treatment in the emergency department could impact the days hospitalized and outcomes positively until the primary endpoint is reached. Over the time of five years, patients meeting the inclusion criteria underwent various assessments with their consent. After completing various questionnaires, a CGA and after drawing blood, the participants were randomized into two groups. One group followed 'usual care', whereas for the proceeding treatment of the second group, an individualized treatment plan according to the CGA-screening was drafted and implemented

into the discharge letter. In addition, the general practitioner of those in the second group was contacted when the patient left the hospital. This approach aimed to smooth the transition from clinical to ambulant treatment and to reduce rehospitalization rates. Another sub-goal of the ZNAge study also assessed the nutritional status through blood drawings as well as a nutrition questionnaire and further the MPI.

In the preliminary analysis, an association between circulating levels of plasma carotenoids to multidimensional frailty with specific, uncommon profiles in emergency settings was found. Possibly, a more adequate analysis through a comprehensive/ nutritional assessment about frailty status and further an enhanced clinical decision making in advanced age could be established compared to usual care. To reach a better understanding of the association between carotenoids and frailty, further analyses on metabolomics and nutritional parameters are ongoing.

5.4. CogLife 1.0 – an ongoing study

Parallel to the previously described trial, another original study was conducted by our research team concerning the prevention of cognitive decline. This study analyzed the interactions between multiple variables, such as the plasma levels of the robust nutrition- and antioxidant defence-related biomarkers, endothelial function, and cognitive performance.

Forty-nine participants (aged 72±6 years) had to meet strict inclusion criteria of being free from significant pathology and underwent multiple testing at the same point in time.

1. Computerized assessment of immediate and delayed recall, attention, verbal learning, divided attention, working memory and executive functions using the CogState Brief Battery (CBB); paper-based cognitive testing included Trail Making Test A/B (TMT A/B), Letter Fluency, and Category Fluency.
2. Endothelial function analysis through the EndoPAT Index and its covariates (the logarithm of the reactive hyperemia index as well as the heart rate variability (HRV)) measured by means of the Peripheral Arterial Tonometry (PAT, Itamar Medical LTD).
3. Self-assessment of overall health (comprehensive geriatric assessment- based multidimensional prognostic index – Selfy-MPI)
4. Plasma metabolomics (Nightingale Health) and High-Performance Liquid Chromatography (HPLC) - based analyses of antioxidant micronutrients (six carotenoids, two tocopherols and retinol).

The CBB's numerous validated computerized cognitive assessments consist of four subtests. Firstly, the Detection Task (DET) evaluates the processing speed concerning information, motor speed and attention. In this test, participants need to respond as quickly as possible to a card being presented on the screen to establish their simple reaction time. Secondly, the Identification Task (IDN) measures visual attention by asking participants to determine as quickly as possible whether the offered card is red. Thirdly, the One-Card Learning Task (OCL) tracks visual memory and learning. In this test, participants have to identify whether the card has been shown previously in the task. The final test is the One-Back Task (ONB), which assesses working memory. Participants evaluate whether the shown card is the same as the immediately previously shown card. In each test, the participants need to respond with "Yes" or "No" as quickly as possible as speed and accuracy are recorded in each test [276].

In a preliminary analysis, various associations were assessed. The Selfy-MPI correlated with category and letter fluency, as well as CogState delayed recall. TMT A was associated with pulse rate and HRV, whereas TMT B correlated with endothelial function. The Metabolomic Mortality Score showed a direct association with pulse and inversely with the plasma concentration of lycopene. All analyses were adjusted for age and gender. More in-depth data is still under evaluation and will be available in the future.

Some aspects of the complex interaction between overall health, micronutrient status, endothelial function and cognitive function were observed. Further studies concerning these findings will be undertaken to investigate the compound interplay between the established connections: the metabolomics mortality score, energy metabolism, endothelial function, heart rhythm and rate, memory performance, as well as lycopene and lutein.

6. Conclusion

The shift in demographics and the worldwide aging population forces us to intensify research in the field of cognitive decline. Multidimensional approaches might be the key to a deeper understanding of the complex processes occurring in the aging brain. Through this future knowledge, more effective ways of prevention and treatment could be established.

Further studies assessing the dietary intake and its effects on the carotenoids as well as on cognition and physical performance are currently being conducted. Significant correlations between cognitive and physical activity, as well as the plasma levels of carotenoids have already shown a promising direction for future research. A combined intervention, including nutritional and physical components, might lead to significant effects on cognition with a background of dementia risk. Therefore, multifactorial lifestyle changes might be the solution to a problem that sooner or later we all must face.

7. References

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8. Supplements

8.1. List of Figures

Figure 1: in Anlehnung an Schmeer C, Kretz A, Wengerodt D, Stojiljkovic M, Witte OW. Dissecting Aging and Senescence-Current Concepts and Open Lessons. Cells. 2019 Nov 15;8(11):1446. doi: 10.3390/cells8111446. PMID: 31731770; PMCID: PMC6912776.

Figure 2: Examples of Selected Cognitive Impairment/Dementia Syndromes, Divided into Two Broad Categories: Neurodegenerative and Non-neurodegenerative

Figure 3: Lakey-Beitia J, Kumar D J, Hegde ML, Rao KS. Carotenoids as Novel Therapeutic Molecules Against Neurodegenerative Disorders: Chemistry and Molecular Docking Analysis. Int J Mol Sci. 2019 Nov 7;20(22):5553. doi: 10.3390/ijms20225553. PMID: 31703296; PMCID: PMC6888440.

Figure 4: Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathol. 2009 Jul;118(1):103-13. doi: 10.1007/s00401-009-0522-3. Epub 2009 Mar 25. PMID: 19319544; PMCID: PMC2853006.

8.2. Supplement 1

Influence of a 12-month structured exercise program on the micronutrient-cognitive fitness-physical fitness association profiles in mild cognitive impairment

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NeuroExercise

1. Introduction

Preventive lifestyle strategies have been proven useful against age-related cognitive decline, but there is still a lack of evidence on the reciprocal relationships between nutrition biomarkers and measures of both cognitive and physical performance.

2. Aim

To fill this gap of knowledge, the relationship of plasma levels of the robust nutrition- and antioxidant defense-related biomarkers carotenoids and tocopherols with both indicators of cognitive and physical performance - within the established field of nutritional cognitive neuroscience - was investigated in a group of persons with mild cognitive impairment (MCI) participating in a structured exercise program at the German Sport University in Cologne, Germany.

3. Methods and Patients

The participants were divided in three different groups: the Stretching and Toning Group (SεT), the Aerobic Exercise Group (AE) and the Control Group (CG). At baseline and after one year all groups underwent cognitive and motoric performance tests as well as blood withdrawal. Through a neuropsychological test battery six different cognitive domains were assessed such as attention, executive function, verbal episodic memory, visual episodic memory, psychomotor function and working memory. Physical fitness was assessed through a collection of different tests: *Physical Fitness Evaluation (PFE), Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire (LAPAQ), Mean number of steps per day, Timed Up and Go (TUG), 30 Seconds Chair Stand (CST) as well as the Hand grip strength in both hands*. Carotenoids including lutein, zeaxanthin, β-cryptoxanthin, lycopene, and α- and β-carotene were analyzed by HPLC with UV/vis detection at 450 nm. A second UV/vis detector was connected in series and set at 325 and 292 nm for quantitation of retinol (vitamin A), and α- and γ-tocopherol (vitamin E), respectively.

Group	Age (years)	Sex (female)
SεT (n=13)	72.9± 4.1	8 (61.5%)
AE (n=13)	74.8± 4.0	3 (23.1%)
CG (n=14)	72.4± 6.6	7 (50.0%)

Abbreviations:
SεT= Stretching and Toning Group; AE= Aerobic Exercise Group; CG= Control Group; PFE= Physical Fitness Evaluation; LAPAQ= Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire; TUG= Timed Up and Go; CST= 30 Seconds Chair Stand; TMT B= Trail Making Test B; ISLT= International Shopping List Task; ISLT Recall= International Shopping List Recall Task; MoCA= Montreal Cognitive Assessment; OBT= One Back Task.

4. Preliminary Results

Correlation	Group	r Value	p Value
Lutein/ Steps per day	SεT	0.605	0.037
Lutein/ CST	SεT	0.002	0.002
Zeaxanthin/CST	SεT	0.798	0.003
ß-Cryptoxanthin/ TUG	AE	-0.651	0.016
ß-Carotene/ CST	SεT	0.858	0.001
α-Tocopherol/ Steps per day	SεT	0.613	0.034

Correlations between lipophilic micronutrients and physical measures after the one-year intervention

Correlation	Group	r Value	p Value
Lycopene/ TMT B	AE	-0.661	0.014
Lycopene/ CogState Detection	AE	-0.731	0.005
α-Carotene/ ISLT	SεT	0.586	0.045
α-Carotene/ ISLT Recall	SεT	0.618	0.032
α-Tocopherol/ MoCA	SεT	-0.614	0.034
α-Tocopherol/ OBT	SεT	-0.681	0.010
α-Tocopherol/ ISLT Recall	SεT	-0.629	0.028

Correlations between lipophilic micronutrients and cognitive measures after the one-year intervention

5. Conclusion

There are profiles of associations between cognitive / physical performance measures and specific lipophilic micronutrients which are independent of nutritional intake and persist longitudinally in prospective intervention trials. These associations are known since several years, but in light of the increasing attention towards the nutritional cognitive neuroscience and carotenoids as cognitive frailty indicators, measures of physical/cognitive fitness and micronutrients should be further implemented in future studies investigating the effects of lifestyle interventions against cognitive and physical impairment.

6. Literatur

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8.3. Supplement 2

Multidimensional frailty and circulating carotenoids in older patients admitted to the Emergency Department

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Introduction

Multidimensional frailty is a critical determinant of prognosis in advanced age and **circulating carotenoids** appear to play a role in the maintenance of **robustness**. Aim of this analysis was to evaluate the **Comprehensive Geriatric Assessment** (CGA)-based **frailty degree** and to investigate its relationship to **carotenoid profiles** in patients admitted to the **Emergency Department** (ED) od a large metropolitan hospital.

Literature: Lancet Frailty Series, 2019; Polidori et al., Redox Biology 2021

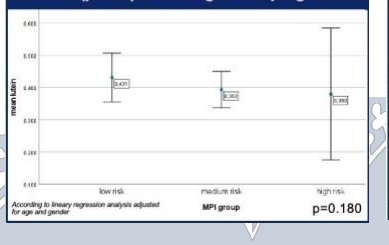
Study design

163 patients admitted to the ED underwent a CGA-based **Multidimensional Prognostic Index (MPI)** calculation - including standardized evaluation of **multimorbidity** (Cumulative Illness Rating Scale), **polypharmacy**, **social** status, **decubitus** risk (Exton-Smith Scale), **cognitive** performance (Short Portable Mental Status Questionnaire), basic and instrumental **Activities of Daily Living** (ADL, IADL), **nutritional** status (Mini Nutritional Assessment) and a blood withdrawal. **Plasma carotenoids** including lutein, zeaxanthin, β-cryptoxanthin, lycopene, α- and β-carotene as well as retinol and α-tocopherol were measured by HPLC with UV/vis detection. Patients were subdivided in robust (MPI-1, score 0-0.33), pre-frail (MPI-2, score 0.34-0.66) and frail (MPI-3, score 0.67-1)- low, medium and high **risk of mortality and other adverse outcomes** at 1 month and 1 year., respectively

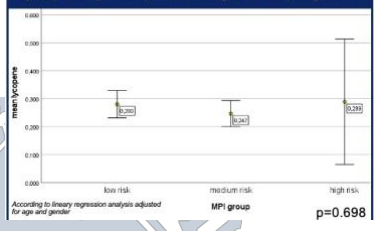
Baseline characteristic

Age mean 76.71 years (SD 6.82)
Gender female n=72 (44.2%)
MPI mean 0.38 (SD 0.16)
MPI-1 n= 70 (42.9%)
MPI-2 n= 86 (52.8%)
MPI-3 n= 7 (4.3%)

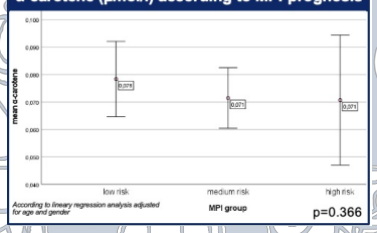
Lutein (µmol/l) according to MPI-prognosis



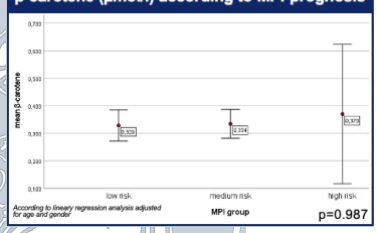
Lycopene (µmol/l) according to MPI-prognosis



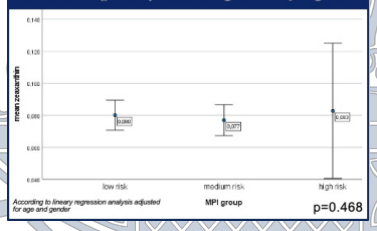
α-carotene (µmol/l) according to MPI-prognosis



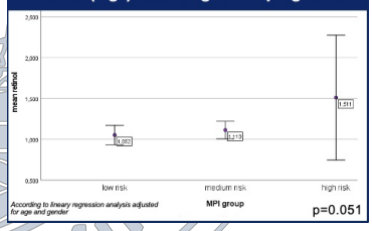
β-carotene (µmol/l) according to MPI-prognosis



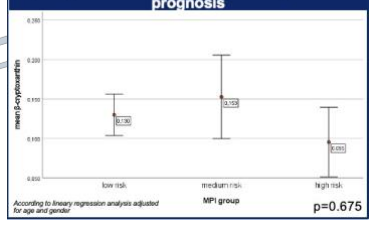
Zeaxanthin (µmol/l) according to MPI-prognosis



Retinol (mg/l) according to MPI-prognosis



β-cryptoxanthin (µmol/l) according to MPI-prognosis



Conclusion

This preliminary analysis shows that circulating levels **of plasma carotenoids appear to be associated to multidimensional frailty** with specific, uncommon profiles in **emergency settings**, where a comprehensive / nutritional assessment may more adequately inform frailty status and clinical decision making in advanced age compared to usual care. Further analyses on metabolomics and nutritional parameters are ongoing to better interpret the shown association between frailty and carotenoids.

8.4. Supplement 3

Main players of the complex interaction between cognitive performance, endothelial function, nutrition, metabolism and overall health

Universität zu Köln
Klinik II
für Innere Medizin
Ageing Clinical Research/ Internal Medicine

Hannah Weigert[1], Johannes Sittig[1], Lena Pickert[1], Wilhelm Stahl[2], Thomas Benzing MD[1,3], Joris Deelen [3,4], M. Cristina Polidori MD FRCP[1,3*]*

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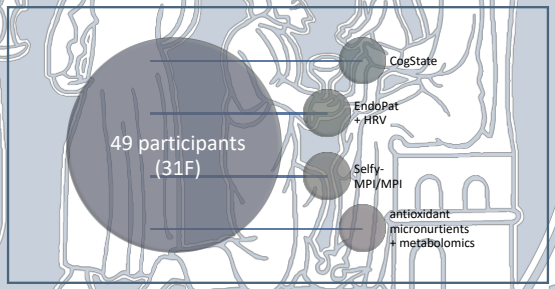
1. Introduction

With progressing age, cognitive performance is increasingly influenced by overall health status, cerebral blood perfusion, metabolism, and redox balance. So far, data on the reciprocal relationship between these components is lacking. Due to the fact, that dementia is not curable, it raises significant concerns in public health.
To address this gap in knowledge, the relationship of plasma levels of the robust nutrition- and antioxidant defense-related biomarkers carotenoids and tocopherols with the endothelial function as well as various test of the cognitive performance was investigated.



2. Methods

Forty-nine participants aged 72±6 years (31F) and free from significant pathology underwent
1. Computerized assessment of immediate and delayed recall, attention, verbal learning, divided attention, working memory, and executive functions using the CogState Battery; paper-based cognitive testing included TMT A/B, Letter Fluency, Category Fluency.

2. Endothelial function's analysis through the EndoPAT Index and its covariates (the logarithm of the reactive hyperemia index as well as the heart rate variability (HRV)) measured by means of the Peripheral Arterial Tonometry (PAT, Itamar Medical LTD).

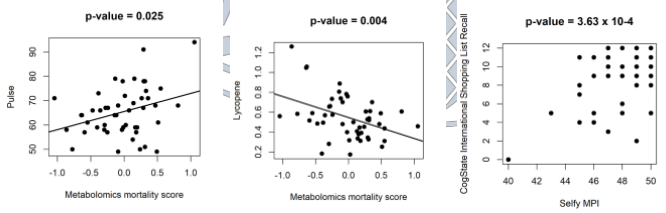
3. Self-assessment of overall health (comprehensive geriatric assessment-based multidimensional prognostic index – Selfy-MPI)

4. Plasma metabolomics (Nightingale Health) and HPLC-based analyses of antioxidant micronutrients (six carotenoids, two tocopherols and retinol).

Statistics are calculated using R. A p-value<0.05 was considered significant.

3. Results*

- The Metabolomic Mortality Score was associated with pulse directly and with plasma concentrations of lycopene inversely (first two left-end plots)
- Memory performance as shown by delayed recall measured by computerized testing was associated with self-assessment of the MPI (right-end plot)



- Plasma lutein levels were associated to endothelial function as shown by the EndoPAT index measured by means of the peripheral arterial tonometry (p=0.039)
- TMT A was significantly associated with pulse rate and heart rate variability (p=0.025), while TMT B was significantly associated with endothelial function (p=0.019)
- The Selfy MPI was associated with letter and category fluency in addition to CogState-based delayed recall (p=0.010 and p=0.022, respectively)

* All analyses were adjusted for age and gender. Moreover, the LN(RHI) and pulse values were adjusted for age, gender, MPI, MNA and Albumin. EndoPAT Index (Ln RHI) was additionally adjusted for HRV_mean, diastolic blood pressure and systolic blood pressure.

Abbreviations: MPI= Multidimensional Prognostic Index; RHI= Reactive Hyperemia Index; HRV= Heart Rate Variability; AI= Augmentation Index; TMT A/ TMT B= Trail Making Test A/B; NB: only significant linear regressions between the variables are displayed;

4. Discussion

In this relatively small but highly characterized sample, some aspects of the complex interplay between cognitive function, endothelial function, micronutrient and overall health status could be observed. Interestingly, the several associations shown in the present investigation concern frequently recurrent parameters in the field of multifactoriality of aging and of nutritional cognitive neuroscience: The metabolomics mortality score, energy metabolism, heart rhythm and rate, endothelial flexibility, memory performance, as well as lutein and lycopene. Further analyses will help disclosing mechanisms underlying the associations found here.

5. Literatur

1. Gerger, P., et al., Associations of Lipophilic Micronutrients with Physical and Cognitive Fitness in Persons with Mild Cognitive Impairment. Nutrients, 2019. 11(4).
2. Nelles, G., et al., Endothelium-mediated changes in vascular tone and cognitive function in patients with subjective cognitive impairment: a pilot study (P7. 114). American Academy of Neurology 2015.
3. Polidori, M.C., W. Stahl, and H.R. Griffiths, Nutritional cognitive neuroscience of aging: Focus on carotenoids and cognitive frailty. Redox Biol, 2021. 44: p. 101996.
4. Deelen, J., et al., A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals. Nat Commun, 2019. 10(1): p. 3346.
5. Aust, O., et al., Analysis of lipophilic antioxidants in human serum and tissues: tocopherols and carotenoids. J Chromatogr A, 2001. 936(1-2): p. 83-93.
6. Norton, S., et al., Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol, 2014. 13(8): p. 788-94.
7. Yuan, C., et al., Dietary carotenoids related to risk of incident Alzheimer dementia (AD) and brain AD neuropathology: a community-based cohort of older adults. Am J Clin Nutr, 2020.
8. Zheng, G., et al., Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment: a systematic review and meta-analysis of randomised controlled trials. British journal of sports medicine, 2016. 50(23): p. 1443-1450.

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8.5. Supplement 4

Circulating Lycopene Levels as Potential Predictors of Cognitive Performance: A Six-Month Follow-Up Study.

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Universität zu Köln
Klinik II
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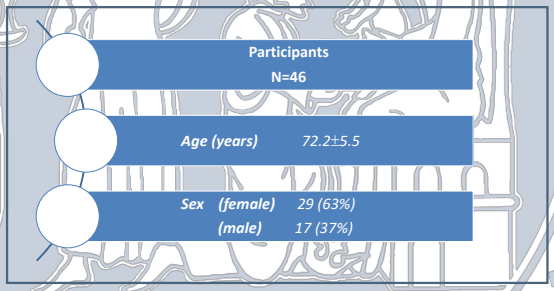
Ageing Clinical Research/
Internal Medicine

1. Introduction

Bioactivity of lipophilic micronutrients is being debated as potential causes of age-related diseases including dementia. Collected evidence suggests these compounds as nutritional determinants of cognitive integrity, but human studies are often severely biased by methodological limitations once cognitive impairment is diagnosed.

To investigate the relationship of plasma levels of the robust nutritional and antioxidant defense-related biomarkers carotenoids and tocopherols with cognitive performance and lifestyle markers long ahead onset of dementia, persons with subjective cognitive impairment (SCI) underwent in-depth phenotyping along with a 6-month follow-up (FU) visit.



2. Methods

Forty-six participants aged 72±6 years (29F) with SCI and free from major clinical diagnoses underwent a broad neuropsychological and clinical assessment. A computerized neuropsychological battery testing delayed recall, attention, verbal learning, divided attention, working memory, and executive functions was performed. Paper&pencil tests included TMT A/B, Letter Fluency, Category Fluency, as well as MoCA.

In-depth clinical and biopsychosocial evaluation included assessments of mobility, nutritional, cognitive, functional and social status, multimorbidity and polypharmacy evaluation as well as calculation of the Multidimensional Prognostic Index (MPI). All participants underwent blood withdrawal for the measurement of metabolomics and of the MetaboHealth panel by NMR-spectroscopy and HPLC-based analyses of antioxidant micronutrients (six carotenoids, two tocopherols and retinol).

A phone FU was undertaken after 6 months to assess health-related quality of life and cognitive status.

The statistics are calculated using R.
A p-value<0.05 was considered significant.

3. Results

Table 1. Significant correlations between MetaboHealth/Clinical parameters and micronutrients

Regression	Beta	SE	p Value
MetaboHealth/Lycopene	-0.76	0.27	**0.007**
MetaboHealth/α-Carotene	-1.5	0.67	**0.030**
MetaboHealth/β-Carotene	-0.36	0.16	**0.030**
SPMSQ FU6/Lycopene	0.97	0.44	**0.032**
MNA-SF/α-Tocopherol	0.10	0.05	**0.029**

Abbreviations: SPMSQ= The Short Portable Mental Status Questionnaire; SPMSQ FU6= The Short Portable Mental Status Questionnaire Follow-Up 6 Months; MNA-SF= Mini Nutritional Assessment – Short Form;

Table 2. Significant correlations between cognitive measures and lipophilic micronutrients

Regression	Beta	SE	p Value
Category Fluency/β-Cryptoxanthin	-6.66	3.17	**0.042**
CogState Identification/β-Cryptoxanthin	0.11	0.04	**0.006**
CogState OBT accuracy/β-Cryptoxanthin	-0.25	0.12	**0.041**

Abbreviations: OBT= One Back Task;

4. Discussion

Among micronutrients, baseline lycopene levels were significantly associated with the MetaboHealth score (p=0.007). Of the micronutrients measured, only lycopene was significantly associated with the test scores of the Short Portable Mental Status Questionnaire (SPMSQ) at six months after baseline (p=0.032). These results are independent of chronological age, sex, and the MPI as a surrogate marker of biological age. Lycopene showed a significant association with the MetaboHealth score at baseline and with the SPMSQ at six months follow-up, possibly indicating to be a potential predictor of cognitive performance. The results are in agreement with previous research and warrant larger-size investigations in healthy persons.

5. Literatur

1. Gerger, P., et al., Associations of Lipophilic Micronutrients with Physical and Cognitive Fitness in Persons with Mild Cognitive Impairment. Nutrients, 2019. 11(4).
2. Pilotto, A., et al. A multidimensional approach to frailty in older people. *Ageing research reviews*, 2020, 60. Jg., S. 101047.
3. Polidori, M.C., W. Stahl, and H.R. Griffiths, Nutritional cognitive neuroscience of aging: Focus on carotenoids and cognitive frailty. Redox Biol, 2021. 44: p. 101996.
4. Deelen, J., et al., A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals. Nat Commun, 2019. 10(1): p. 3346.
5. Aust, O., et al., Analysis of lipophilic antioxidants in human serum and tissues: tocopherols and carotenoids. J Chromatogr A, 2001. 936(1-2): p. 83-93.
6. Norton, S., et al., Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol, 2014. 13(8): p. 788-94.
7. Yuan, C., et al., Dietary carotenoids related to risk of incident Alzheimer dementia (AD) and brain AD neuropathology: a community-based cohort of older adults. Am J Clin Nutr, 2020.
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9. Attachment

9.1. List of Publications

9.1.1. Publications (as first author)

Weigert H, Stuckenschneider T, Pickert L, Rossi A, Meyer AM, Nelles G, Schulz RJ, Stahl W, Schneider S, Polidori MC; NeuroExercise Study Group. Influence of a 12-Month Structured Exercise Program on the Micronutrient-Cognitive Fitness-Physical Association Profiles in Mild Cognitive Impairment. J Alzheimers Dis Rep. 2022 Nov 22;6(1):711-722. doi: 10.3233/ADR-220039. PMID: 36606208; PMCID: PMC9741747.

9.1.2. Publications (as co-author)

Gerger P, Pai RK, Stuckenschneider T, Falkenreck J, Weigert H, Stahl W, Weber B, Nelles G, Spazzafumo L, Schneider S, Polidori MC. Associations of Lipophilic Micronutrients with Physical and Cognitive Fitness in Persons with Mild Cognitive Impairment. Nutrients. 2019 Apr 22;11(4):902. doi: 10.3390/nu11040902. PMID: 31013604; PMCID: PMC6520910.

Falkenreck JM, Kunkler MC, Ophey A, Weigert H, Friese A, Jahr P, Nelles G, Kalbe E, Polidori MC. Effects of the Multicomponent Cognitive Training Program BrainProtect in Cognitively Healthy Adults: A Randomized Controlled Trial. J Alzheimers Dis. 2023 Jun 29. doi: 10.3233/JAD-220619. Epub ahead of print. PMID: 37393493.

Sittig J, Pickert L, Weigert H, Deelen J, Polidori MC, Nelles G. Relationship Between Endothelial Function, Vital Parameters, and Cognitive Performance in Community Dwellers with Subjective Cognitive Decline: An Observational Study with Six Months Follow Up. J Alzheimers Dis. 2024;100(s1):S13-S24. doi: 10.3233/JAD-240661. PMID: 39150830.

9.1.3. Poster Presentations (as first author)

Weigert et al.: Main players of the complex interaction between cognitive performance, endothelial function, nutrition, metabolism, and overall health

– Design und vorläufige Ergebnisse der Studie CogLife 1.0; (DGIM conference in Wiesbaden, April 2022) (Supplement 3)

Weigert et al.: Circulating Lycopene Levels as Potential Predictors of Cognitive Performance: A Six-Month Follow-Up Study. (Modifying Cardiovascular Ageing: from old cells to elderly patients, Halle, September 2023) (Supplement 4)