Aus dem Zentrum für Innere Medizin der Universität zu Köln
Klinik und Poliklinik für Innere Medizin II der Universität zu Köln
Direktor: Universitätsprofessor Dr. med. Th. Benzing

Profiles of lipophilic micronutrients are associated with cognitive and physical fitness in patients with mild cognitive impairment

Inaugural-Dissertation zur Erlangung der Doktorwürde
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von
Perihan Gerger

promoviert am 15. September 2025

Gedruckt mit Genehmigung der Medizinischen Fakultät der Universität zu Köln
Druckjahr 2025

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Die dieser Arbeit zugrundeliegenden Daten der klinischen Studie wurden von mir in Zusammenarbeit mit Frau Professorin Dr. Dr. M. Cristina Polidori, Leiterin des Schwerpunktes für klinische Altersforschung der Klinik II für Innere Medizin der Uniklinik Köln, Köln, Deutschland entwickelt.

Die Erhebung dieser Daten wurde in Zusammenarbeit mit Herrn Tim Stuckenschneider, Frau Heide Krahl und Frau Roopa Pai an der Deutschen Sporthochschule Köln, an der Universitätsklinik Düsseldorf sowie an der Universitätsklinik Bonn im Rahmen der Neuroexercise-Studie vorgenommen. Eine genaue Darstellung des Eigenanteils kann meiner schriftlichen Erklärung des geleisteten Beitrages des Doktoranden eingesehen werden, welche von allen Mitautoren unterschrieben wurde.

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Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisor, Professor Dr. Dr. M. Cristina Polidori for her guidance, support and trust at every stage of this project. Her passion for gerontology and geriatric patients has inspired and motivated me ever since I met her.

I am also grateful to my colleagues and research team for their support, and help in both larger and smaller aspects of this journey.

Above all, I want to express my gratitude to my family and the friends around me. My thankfulness goes to my parents, Kadriye and Feridun; my siblings, Melis and Bersan; and my dearest friend Elif; as well as so many more I cannot mention by name here, but have helped me in countless ways. I cannot thank them enough for their consistent motivation and attention throughout my years of study.

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Abbreviations

AA Ascorbic Acid

AD Alzheimer´s Disease

ADI Alzheimer's Disease International

ADLs activities of daily living

APOE Apolipoprotein E

BMI Body mass index

BDNF Brain-derived neurotrophic factor

CAT catalase

CD 4 Cluster of differentiation 4

CI Confidence interval

CNS Central nervous system

CRP C-reactive Protein

CSF Cerebrospinal fluid

CVD Cardiovascular disease

DASH Dietary Approaches to Stop Hypertension

EGCG Epigallocatechin-3-gallate

FNDC5 Fibronectin Type III Domain Containing 5

GPx glutathione peroxidase

GR glutathione reductase

GSH glutathione

GSSG generate glutathione disulfide

HR Hazard ratio

HANDLS Healthy Ageing in Neighbourhoods of Diversity across the Life Span

HPLC High performance liquid chromatography

ISLT International Shopping List Task

KAP Cologne Alzheimer Prevention Center

MCI Mild Cognitive Impairment

MeDi Mediterreanean diet

MIND Mediterreanean-DASH Intervention for Neurodegenerative Delay

NCD Non-communicable disease

RCTs Randomized controlled trials

RNS Reactive nitrogen species

ROS Reactive oxygen species

RONS Reactive oxygen and nitrogen species

RR Relative Risk

SCI subjective cognitive impairment

SOD superoxide dismutase

TBI Head injuries

The FINGER Study The Finnish Geriatric Intervention Study To Prevent Cognitive Impairment and Disability

Trx Thioredoxin

TNF- α Tumour Necrosis Factor Alpha

TUG-Test Timed Up and Go Test

OXPHOS oxidative phosphorylation system

PUFAs Polyunsaturated fatty acids

PAR population-attributable risk

WHO World Health Organization

1. Deutsche Zusammenfassung

Mit zunehmender Lebenserwartung gewinnt die Prävention altersbedingter kognitiver Beeinträchtigungen, insbesondere der leichten kognitiven Störung (MCI) und Demenz, mit der Alzheimer-Krankheit als ihre häufigste Form, zunehmend an Bedeutung. Diese Herausforderungen betreffen nicht nur die individuelle Gesundheit und Lebensqualität der Betroffenen, sondern haben auch weitreichende Auswirkungen auf Familien, das Gesundheitssystem und die Gesellschaft als Ganzes [1].

Da bisher keine definitive Heilung der Demenz verfügbar ist, rücken modifizierbare Lebensstilfaktoren wie körperliche Aktivität und Ernährung in den Fokus präventiver Strategien [2]. Speziell lipophile Mikronährstoffe wie Carotinoide und Tocopherole gelten aufgrund ihrer antioxidativen Eigenschaften als potenzielle Schutzfaktoren gegen kognitive und körperliche Abbauprozesse im Alter. Dennoch ist wenig darüber bekannt, wie deren Plasmaspiegel mit funktionellen Parametern bei Personen mit MCI zusammenhängen. Ziel der vorliegenden Arbeit war es daher, Zusammenhänge zwischen Plasmaspiegeln spezifischer lipophiler Mikronährstoffe und der kognitiven sowie körperlichen Leistungsfähigkeit bei älteren Menschen mit MCI zu untersuchen.

Im Rahmen der vom EU Joint Programme – Neurodegenerative Disease Research (JPND) geförderten multizentrischen NeuroExercise-Studie, die sich der Entwicklung evidenzbasierter Präventionsstrategien gegen neurodegenerative Erkrankungen widmet, wurden 56 Personen mit leichter kognitiver Beeinträchtigung (MCI) am Standort Deutsche Sporthochschule Köln rekrutiert und umfassend hinsichtlich kognitiver, physischer sowie ernährungsbezogener Parameter untersucht. Teilnahmeberechtigt waren Personen mit der Diagnose einer leichten kognitiven Beeinträchtigung (MCI). Ein MoCA-Gesamtscore zwischen 18 und 26 diente dabei als operationales Maß zur Identifikation kognitiver Einschränkungen. Weitere Einschlusskriterien umfassten stabile gesundheitliche Verhältnisse über mindestens sechs Monate sowie das Fehlen einer manifesten Demenzdiagnose. Neben neuropsychologischen Tests wie der computergestützten CogState-Testbatterie (z. B. International Shopping List-Test) und klassischen Verfahren wie dem Trail Making Test und Wortflüssigkeitstests, wurden funktionelle körperliche Parameter wie die Mobilität (Timed Up and Go-Test) und tägliche Schrittzahl erfasst. Zur Erhebung der Ernährungsgewohnheiten diente ein standardisierter Fragebogen, während die Plasmakonzentrationen von sechs Carotinoiden und zwei Tocopherol-Isoformen mittels HPLC bestimmt wurden. Die statistische Analyse erfolgte mittels partieller Korrelationen unter Kontrolle der Obst- und Gemüseaufnahme [3].

Die Plasmaspiegel spezifischer lipophiler, antioxidativer Mikronährstoffe zeigten signifikante positive Korrelationen mit der kognitiven und körperlichen Leistungsfähigkeit von Personen mit leichter kognitiver Beeinträchtigung. Insbesondere waren Lutein, Zeaxanthin, βCryptoxanthin und β-Carotin signifikant mit der Gedächtnisleistung im CogState ISLT assoziiert ($p < 0,01$).

Darüber hinaus korrelierten höhere β-Cryptoxanthin-Spiegel invers mit den Ergebnissen im Timed Up & Go (TUG) Test (niedrigere TUG-Zeit; $p < 0,05$), was auf eine bessere Mobilität hinweist. γ-Tocopherol zeigte eine positive Korrelation mit der Anzahl täglich zurückgelegter Schritte ($p < 0,01$). In einer explorativen Subanalyse wurde eine Teilnehmergruppe mit durchgängig über dem Median liegenden Plasmakonzentrationen aller untersuchten Mikronährstoffe identifiziert (bezeichnet als ‚Gruppe mit hohem Mikronährstoffprofil'), die signifikant besseren kognitiven und physischen Leistungen erzielte als die übrige Kohorte.

Diese Ergebnisse unterstreichen die mögliche Rolle lipophiler Mikronährstoffe als unabhängige Marker und potenzielle Einflussfaktoren für kognitive und körperliche Gesundheit im Alter. Die Assoziationen traten auch nach Kontrolle der Ernährungsgewohnheiten auf, was auf eine eigenständige Bedeutung der Mikronährstoffe hindeutet. Die beobachteten Zusammenhänge passen zu bisherigen Erkenntnissen aus der Nutritional Cognitive Neuroscience, insbesondere zur Rolle von Lutein und Zeaxanthin im Gehirnstoffwechsel. Die Arbeit liefert somit wichtige Hinweise auf das präventive Potenzial ausgewählter Mikronährstoffe in der multidimensionalen Demenzprävention. Weitere longitudinale und interventionelle Studien sind notwendig, um Kausalitäten zu klären und personalisierte Ernährungskonzepte zur Erhaltung der kognitiven und körperlichen Funktionen im Alter zu entwickeln.

2. Summary

With increasing life expectancy, the prevention of age-related cognitive impairments, particularly mild cognitive impairment (MCI) and dementia—with Alzheimer's disease (AD) as the most common form—has gained growing importance. These challenges affect not only the individual health and quality of life of those affected, but also have far-reaching implications for families, the healthcare system, and society as a whole [1].

As there is currently no definitive cure for dementia, modifiable lifestyle factors such as physical activity and nutrition are increasingly the focus of preventive strategies [2]. In particular, lipophilic micronutrients such as carotenoids and tocopherols are considered potential protective factors against age-related cognitive and physical decline, due to their antioxidant properties. However, little is known about how their plasma levels relate to functional parameters in individuals with MCI. Therefore, the present study aimed to examine the associations between plasma concentrations of specific lipophilic micronutrients and both cognitive and physical performance in older adults with MCI.

As part of the multinational NeuroExercise Study—funded by the EU Joint Programme – Neurodegenerative Disease Research (JPND), which aims to develop evidence-based

strategies to address the challenge of neurodegenerative diseases—56 individuals with MCI were recruited at the site of the German Sport University Cologne and comprehensively assessed with regards to cognitive performance, physical function, and nutritional biomarkers. Eligible participants were individuals diagnosed with MCI. A Montreal Cognitive Assessment (MoCA) score between 18 and 26 served as an operational criterion for cognitive impairment. Additional inclusion criteria required a stable medical condition for at least six months and the absence of a diagnosis of manifest dementia. In addition to neuropsychological testing—such as the computer-based CogState test battery (e.g. International Shopping List Task) and classical methods including the Trail Making Test and verbal fluency tasks—functional physical parameters such as mobility (Timed Up and Go test) and daily step count were recorded. Dietary habits were assessed using a standardised questionnaire, and plasma concentrations of six carotenoids and two tocopherol isoforms were measured using HPLC. Statistical analyses were performed using partial correlations, controlling for fruit and vegetable intake [3].

Plasma levels of specific lipophilic antioxidant micronutrients showed significant positive associations with cognitive and physical performance in individuals with MCI. Specifically, lutein, zeaxanthin, β-cryptoxanthin, and β-carotene were strongly correlated with verbal memory performance, as measured by the CogState ISLT ($p < 0.01$). Furthermore, βcryptoxanthin levels were inversely associated with Timed Up & Go (TUG) scores ($p < 0.05$), indicating better mobility, and γ-tocopherol levels were positively correlated with the number of daily steps ($p < 0.01$). An exploratory sub-analysis identified a subgroup of participants with consistently above-median plasma concentrations for all assessed micronutrients (referred to as the ‘high micronutrient profile group’), who showed significantly better physical and cognitive performance compared to the remaining cohort.

These findings highlight the potential role of lipophilic antioxidant micronutrients as independent markers and possible modulators of cognitive and physical health in ageing. The associations between plasma concentrations of specific carotenoids and tocopherols and cognitive (ISLT) as well as physical (TUG, daily steps) performance remained statistically significant after adjusting for fruit and vegetable intake. This adjustment was applied to isolate the specific effects of micronutrient status from the broader influence of general dietary habits, as fruit and vegetable intake serves as a validated proxy for antioxidant-rich food consumption. Thus, the results suggest that the observed correlations are independent of general dietary patterns and may reflect direct biological effects of individual micronutrients. These findings are consistent with current insights from nutritional cognitive neuroscience, particularly with regard to the preferential accumulation and neuroprotective role of lutein and zeaxanthin in brain metabolism. This study provides important evidence for the preventive relevance of specific lipophilic micronutrients within multidomain strategies to preserve cognitive and physical function in ageing. Nonetheless, longitudinal and interventional studies are needed to

clarify causality and to guide the development of personalised nutritional approaches for maintaining cognitive and physical function in old age.

3. Introduction

In recent years, the international research community has reached a growing consensus: dementia is not an inevitable consequence of ageing but a largely preventable syndrome—provided that modifiable risk factors are targeted systematically and early enough. As reported by the 2024 Lancet Commission on Dementia Prevention, Intervention and Care [4], addressing twelve modifiable risk factors across the life course could potentially prevent up to 45% of dementia cases. These include educational attainment, physical inactivity, poor diet, hypertension, hearing loss, social isolation, and depression, among others. This shift in perspective has marked a turning point: from a passive to a proactive approach in cognitive health research.

Building on this paradigm, an increasing number of multidomain intervention studies have been initiated to simultaneously address several of these risk factors. Pioneering work in this field has been conducted by Kivipelto and colleagues through the FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) [51]. It demonstrated that a structured combination of nutritional guidance, physical activity, cognitive training and vascular risk monitoring can significantly slow cognitive decline in older adults at risk. The international adaptation of this model—the WW-FINGERS network—is currently expanding this evidence base across different populations and healthcare settings.

In the field of nutrition, large-scale cohort studies such as HELIAD and ALBION have substantially contributed to our understanding of the relationship between dietary habits and cognitive trajectories. The HELIAD study (Hellenic Longitudinal Investigation of Ageing and Diet) is a population-based, multidisciplinary cohort study conducted in Greece—a country traditionally adhering to MeDi patterns [36]. Its aim is to evaluate the prevalence and incidence of dementia, MCI, and other neuropsychiatric conditions, while exploring their associations with diet, lifestyle, and sociodemographic factors. With over 1,000 participants aged 65 and above, HELIAD provides valuable insights into how MeDi adherence affects cognitive trajectories in a Mediterranean population. Notably, the study found that more than one third of participants were at high risk for malnutrition, and that red meat consumption was elevated while intake of key MeDi components—such as legumes, vegetables, and nonrefined grains—was below recommended levels. The HELIAD cohort also serves as an important reference for culturally sensitive cognitive norms and MeDi scores, enhancing its relevance for cross-cohort comparisons. The ALBION study (Aiginition Longitudinal Biomarker Investigation of

Neurodegeneration) is of particular relevance due to its integration of nutritional profiles, biomarker classification (AT(N)), and longitudinal clinical diagnoses [5,6]. Alongside this, Scarmeas and colleagues have highlighted the role of adherence to the MeDi as a protective factor against frailty [7] and dementia incidence [8], reinforcing its role as a nutritionally dense, neuroprotective dietary pattern. The findings of this study emphasise the significance of dietary interventions as a modifiable component in the prevention of dementia and support its integration into comprehensive, multidomain prevention strategies. Parallel to this, physical activity has emerged as one of the most consistently supported preventive strategies. In their review titled “A Growing Consensus” [9], the authors emphasise that exercise interventions not only enhance cardiovascular health, but also modulate neuroinflammation, support synaptic plasticity, and may improve cerebral blood flow and metabolism. Despite some heterogeneity in intervention outcomes, the biological plausibility and consistency of observational data have led to international recommendations promoting regular moderate-to-intense exercise throughout life.

As for cognitive training, while early interventions such as those from Pitkälä et al. [10,11] laid the groundwork, digital tools like NeuroNation and Neurovitalis are now at the forefront of scalable cognitive enhancement. Recent studies further support this, demonstrating that structured cognitive interventions such as BrainProtect® can induce long-lasting improvements in executive function and memory—even up to 12 months post-intervention [12].

Altogether, these findings strengthen the rationale for a comprehensive, lifestyle-based prevention model that is personalised, evidence-based, and integrative. The following section introduces the emerging discipline of Nutritional Cognitive Neuroscience, which serves as a neurobiological and behavioural bridge between nutrition, brain function, and ageing trajectories.

3.1. Nutritional cognitive neuroscience

Nutritional Cognitive Neuroscience has recently been emerged as an interdisciplinary field with the aim to systematically investigate the influence of nutrition on cognitive function and brain health [22]. Growing evidence indicates that nutrition affects both brain structure and function. This applies to overall dietary patterns as well as to specific micronutrients, with important implications for understanding mechanisms of healthy brain ageing. Research within the domain of Nutritional Cognitive Neuroscience has provided valuable contributions to this expanding scientific field, particularly through studies exploring underlying pathophysiology and the effects of dietary interventions [23-25].

The field has recently attracted increased scientific attention, primarily due to two key aspects, both related to the significant demographic transition with the rising number and proportion of the older population. The first is the increasing need to preserve cognitive integrity for healthy and active ageing, with both mental and physical resilience [26,27]. The second aspect is the growing prevalence of, and focus on age-related cognitive impairments, such as mild cognitive impairment (MCI) [26, 26, 28] and AD. Cognitive impairment has been highlighted as a public health priority, with no known cure for dementia. The underlying pathophysiology of dementia is multifaceted, known as multifactoriality, which is increasing with advanced age. As the processes leading to dementia start decades prior to dementia onset [29,30], it is pivotal to shift the attention towards early diagnosis of cognitive changes and slow down their progression with preventive strategies. Previous studies on the role of lifestyle- and vascular-related preventive strategies have demonstrated that vascular risk control and lifestyle improvements can effectively slow down the progression of cognitive impairment [23,24,31-33].

There is growing evidence on the crucial role of quantitatively and qualitatively adequate dietary intake as nutrition is a modifiable lifestyle factor, suggesting an association between nutrition and brain health [36]. Traditional research in nutritional epidemiology has historically examined cognitive health in relation to individual nutrients, which has substantially changed to start focusing on the multifaceted synergistic interactions among nutrients. Although research on specific nutrients is scientifically valid providing crucial evidence on the mechanisms by which nutrition impacts health and the risk of dementia [37], the recent switch targeting the multifaceted, synergistic interplay among a micronutrient network, has promoted emerging interest in the actions of whole dietary patterns [38].

Dietary patterns reflect the overall quality and composition of habitual food and nutrient intake, and may serve as stronger indicators of cognitive function and brain health than isolated dietary components [39]. The Mediterranean Diet (MeDi) is the most intensively studied pattern, characterised by a selection of foods rich in beneficial nutrients, including olive oil that provides polyphenols and monounsaturated fatty acids [40], fish that delivers omega-3 polyunsaturated fats and vitamin D, and fruits and vegetables that provide vitamins C and E, carotenoids and folate [41]. In multiple recent population studies, the MeDi has been linked to slower cognitive decline, decreased risk of AD, a lower rate of progression from MCI to AD, and reduced mortality in patients with AD [42,43,44] Furthermore, the findings of these epidemiological investigations have been corroborated by systematic reviews and meta-analyses, demonstrating that adherence to MeDi is associated with a reduced risk of cognitive decline, MCI, AD, and progression from MCI to AD [45,46]. As previously demonstrated by Tanaka et al., MeDi is increasingly recognised for its protective role in sustaining cognitive health over the long term. This benefit is hypothesised to result from the diet's favourable influence on vascular function as well as its antioxidant and antiinflammatory properties, which together

may mitigate key pathways involved in cognitive decline [47]. In a recent Randomised Control Trial with 6.5 years of follow-up, nutritional intervention with an improved MeDi—including extra virgin olive oil or nuts—appeared to enhance global cognition, attributed the effectiveness mostly to extra virgin olive oil. Another recent study analysed whether following a MeDi relates to cognitive function and their in vivo biomarkers, beta-amyloid plaques and tau-protein, corroborating MeDi as a protective factor against cognitive decline and mediotemporal atrophy, which might be explained by a decrease of amyloidosis and tau pathology [48]. Furthermore, the FINGER study, an ongoing trial on lifestyle modification, demonstrated that a multidomain intervention— comprising nutritional guidance (particularly adherence to the MeDi), physical exercise, cognitive training, and social engagement—can significantly enhance overall cognitive performance and slow cognitive decline in older adults at risk [49-51].

Moreover, previous research has demonstrated that distinct dietary patterns may induce specific cardiometabolic and neurocognitive effects. The Dietary Approaches to Stop Hypertension (DASH diet) , which emphasises the consumption of nutrient-rich, low-sodium foods, has been associated with reductions in blood pressure and improvements in psychomotor performance [52]. Building on the complementary benefits of the DASH and Mediterranean diets, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND diet) was developed as a targeted nutritional strategy aimed at delaying neurodegenerative decline. Adherence to the MIND diet is characterised by increased consumption of green leafy vegetables and berries—both considered neuroprotective—alongside limited intake of foods high in saturated fats and animal-derived products [53]. This dietary pattern has been linked to a deceleration of age-related cognitive decline, particularly in domains such as semantic and episodic memory, as well as perceptual processing speed [20]. Evidence from prior research suggests that adherence to dietary patterns such as the Mediterranean, DASH, and MIND diets may contribute to the preservation of brain health by counteracting age-related neurodegenerative processes. This has led to growing interest in the application of blood-based biomarkers to better characterise the mechanisms through which these dietary patterns exert their neuroprotective effects in the context of brain ageing [22].

The influence of nutrition on brain health is increasingly recognised as a complex and multifactorial process, shaped by the combined actions of multiple nutrients rather than isolated components. Nutritional epidemiology has demonstrated that dietary patterns consist of interrelated nutrients whose interactive effects may significantly impact various aspects of brain ageing. In response, the interdisciplinary field of Nutritional Cognitive Neuroscience has developed methodological frameworks to identify nutrient constellations that best reflect these synergistic influences [22]. Recent findings in cognitive neuroscience suggest that brain ageing is a multifaceted and individually variable process, characterised by widespread structural and

functional alterations. To accurately capture these changes, advanced neuroimaging techniques with high spatial resolution have been developed. In this context, methodological approaches that account for interindividual variability in both dietary intake and neural ageing trajectories are gaining increasing relevance. It is assumed that the integration of such approaches may enable the identification of specific nutrient patterns associated with healthy cognitive ageing [22].

Within the field of nutritional cognitive neuroscience, increasing attention is being directed towards the development of personalised nutritional strategies that reflect individual variability in both dietary status and brain health. The overarching objective of such approaches is to enhance the accuracy and relevance of nutritional interventions, and to support novel avenues for promoting mental health, facilitating healthy cognitive ageing, and addressing diet-related disease risk. [21].

In our present study, a broad spectrum of the most robust biomarkers of nutrition and antioxidant defence in clinically highly characterised patients comprehensively assessed in terms of both cognitive and physical performance—an approach that, to our knowledge, have not yet been explored in previous studies. In particular, the use of a large battery of neuropsychological tests including a validated, accurate gamified computerised testing with high clinimetric properties (CogState), enables a detailed description of the association between selected micronutrients and specific cognitive abilities. This represents a further step in the field of nutritional cognitive neuroscience [22]. The interdisciplinary field of Nutritional Cognitive Neuroscience plays a pivotal role in advancing our understanding of how nutrition supports brain health in the context of ageing. This growing body of evidence provides a foundation for the development of targeted nutritional interventions aimed at mitigating cognitive decline in older adults [22].

3.2. Burden of cognitive impairment

The rapidly growing demographic changes, coupled with a tremendous increase in ageing population, thus unavoidable increase of certain age-related diseases including neurodegenerative diseases in general and dementia in particular [26,27], causes a major public health concern, affecting around 55 million people worldwide. There are nearly 10 million new cases every year and this figure is estimated to triple by 2050 [52].

Dementia is a major cause of disability and loss of independence in older age, often imposing a substantial burden not only on those affected, but also on their families and informal caregivers. While there is no cure for dementia, attention is shifted towards need of a proactive management of modifiable risk factors to prevent or slow down the progression of cognitive

decline. By 2030, it is estimated that around 78 million individuals will be living with dementia. Health professionals—including general practitioners, neurologists and geriatricians—will be increasingly confronted with diagnostic, therapeutic and socioeconomic challenges, particularly in less developed and low-income regions, where approximately 70% of all cases are expected to occur [52].

The impact of dementia on population health in terms of incidence and prevalence occurred in the past recent years, with prevalence of dementia growing exponentially with advanced age [55], and doubles every five years of age after age 65. In high-income countries, the prevalence of dementia among individuals aged 65 and older ranges from 5-10%. Rates are typically higher in women, largely due to their longer life expectancy compared to men. By 2050, the prevalence of dementia is expected to double in Europe and triple worldwide, and that assessment is 3 times higher when based on a biological (rather than clinical) definition of AD [56]. The incidence of dementia grows consistently until age 85 or 90, and then continues to increase but at a reduced rate. It is either similar in men and women or slightly higher in women [57]. Recent Projections for Germany suggest that the number of individuals affected by dementia will continue to rise until 2070. This increase is expected to follow the ageing and passing of the baby-boom generation born in the 1950s and early 1960s, unless effective preventive measures are implemented or novel therapeutic options are established
[58].

Dementia significantly impairs a person´s ability to maintain the activities of daily living. It is often associated with personality change, behavioral symptoms, and numerous clinical complications. It also increases the risk of bone fractures, pneumonia, or urinary tract infections, and most significantly, dependence on nursing care [57]. With Dementia being the leading cause of care dependency, disability [59,60] and high multimorbidity, it is one of the most expensive disease groups affecting adults aged 65 and older [61]. On a global scale, the measurable socioeconomic costs of dementia are overwhelming. In 2019, the global economic burden of dementia was estimated at US$1.3 trillion, with projections suggesting an increase to US$2 trillion per year by 2030. When adjusted for rising care-related costs, total global expenditure may reach as much as US$2.8 trillion by that time.

As the demand for dementia care grows rapidly around the world, it places a considerable burden on caregivers [62]. The vast majority of whom are cared for by family members in the community [64] are confronted with both instrumental challenges—attending to the needs and symptoms of patients—and emotional challenges, coping with a loved one's progressive deterioration, as well as their own loss of autonomy, increased social isolation, reduced life expectancy, and financial burdens. As a result, caregivers typically show higher rates of stress and depression [65], poorer physical health, higher risk of developing cardiovascular diseases, especially hypertension [66-68], and reduced levels of employment compared to the general

population [69,70]. In a 3-year longitudinal study across nine memory clinics, researchers found that patient characteristics, such as neuropsychiatric symptoms, the degree of functional impairment, inability to drive, and fewer medications, and the extent of services and caregiver gender predicted overall burden [71], which is in agreement with prior studies [72,73,74,75].

Furthermore, previous studies found out, the length of time providing care on a day-to-day basis, an objective burden indicator, is one of the most consistent predictors of subjective burden and depression [76,77,78,79]. To assess the length of time providing care, in 2019, informal caregivers of people living with dementia provided more than 89 billion hours of assistance with Activities of daily living (ADLs), corresponding to an average of around five hours of care per day for each affected individual.

In conclusion, there is a large body of evidence demonstrating, that the most effective way to reduce the global burden of dementia in ageing societies and associated costs in the future, is by taking an approach that seeks to implement the evidence we have for each stage of the life course, with particular focus on protective factors in early, mid- and later life, adequate availability of improved diagnostics and holistic treatment for individuals whose lives are impacted by dementia and those around them and, finally, avoiding interventions that reduce the quality of life towards its end [80].

3.3. Preventive measures of cognitive impairment

Age-related cognitive decline has been the subject of a large body of research aimed at identifying the most effective preventive strategies. Exploring the field of dementia prevention, we come across a pivotal and multifaceted aspect of public health policy, with the World Health Organisation (WHO) and Alzheimer's Disease International (ADI) considering dementia a global public health priority [81]. Given the increasing number of dementia cases worldwide, to prevent or delay the onset of dementia, and particularly because of the absence of definitive curative treatments [82], there is growing need and evidence of risk factors for dementia, which shows that vascular- and lifestyle-related preventive measures— such as the control of vascular risk factors and lifestyle changes—can contribute to delaying its onset [33,86].

Prevention can be implemented as part of a multidimensional approach, and if adopted in early adulthood, it has a higher chance of success. Primary dementia prevention aims to reduce the risk of developing the condition by targeting modifiable risk factors before the onset of biological changes. In contrast, secondary prevention is concerned with the early detection of disease during its asymptomatic phase [87]. To prevent dementia progression, several risk factors need to be considered [88], some of which are non-modifiable, including genetic influences [89], gender and age. The attention is shifted towards the detection and modification

of those factors which have a large potential to be modified before the onset or during the course of the disease [87].

The main non-modifiable risk factor for dementia and AD is age [90], two-thirds of patients with dementia are over 75 years of age. The aged population over 75 is not only frequently affected by dementia, but also by multimorbidity. Multimorbidity may affect up to 70% of the population between 50 and 94 years of age, and over 80% of the oldest-old population [133]. Multimorbidity and dementia in older subjects are associated with loss of function, increased mortality and a high hospitalisation rate and the Hazard Ratio (HR) for all-cause mortality increases with the number of comorbidities up to 6.9 for three comorbidities [91]. In both, dementia and AD, incidence and prevalence follow an exponential increase after the age of 65, and nearly double every five years from 65 to 90 years. Studies on the incidence of dementia/AD after the age of 90 have more heterogeneous results, reporting a steady increase or a plateau [92].

Another non-modifiable risk factor is biological sex, with higher occurrence of dementia in women compared to men, which is possibly related to a higher life expectancy as well as menopause and the associated drop in sex hormones [93]. The effects of hormone replacement therapy, which is partially protective, but also risk-increasing, have been shown in numerous epidemiological and clinical studies. Those findings have been summarised in a recent American consensus, which concluded that there is no indication for hormone replacement therapy for the prevention of dementia [94].

Furthermore, familial history of AD or dementia, with first-degree relatives of AD patients having a higher lifetime risk of developing AD than the general population or relatives of nondemented individuals. Familial clustering of dementia cases may result from genetic predispositions, environmental influences, or the interaction between the two. Among the best-established genetic risk factors for late-onset dementia and Alzheimer’s disease is the ε4 allele of the apolipoprotein E (APOE) gene. [83].

The traditional classification of preventive measures is only partially applicable in the context of neurodegenerative diseases such as dementia. This is partly due to the fact that certain risk factors—such as hypertension—are both disease-related and serve as targets for preventive intervention [95]. Moreover, many forms of dementia are characterised by an extended preclinical phase, which further complicates the distinction between different levels of prevention. In Alzheimer’s disease, for example, cognitive decline is often preceded by neurodegenerative processes lasting two to three decades, during which no clinical symptoms are yet detectable. Other diseases causing dementia (neurodegenerative, cerebrovascular) can also have pre-clinical stages, during which the affected person has no or subtle cognitive

manifestations. Thus, cognitively normal older adults represent a heterogeneous group (i.e., from no/minimal brain lesions to various degrees of brain pathology burden), and prevention of cognitive impairment and dementia in this age group entails a combination of primary and secondary prevention [83].

A large number of mechanisms related to AD genetics, different modifiable risk factors, and protective factors have been identified. According to the 2024 report by Livingston et al. for the Lancet Commission on Dementia Prevention, Intervention and Care, up to 45 % of dementia cases are estimated to be attributable to twelve modifiable risk factors across the lifespan, and could potentially be prevented or delayed through targeted interventions [4]. The WHO guidelines provide guidance on key pillars of prevention, including four main lifestyle domains: cognitive training, social activity, nutrition and physical activity, which can effectively counteract the decline in cognitive function. The guidelines are divided into the categories of chronic diseases, modifiable risk factors and protective factors [95].

Modifiable risk and protective factors of dementia and AD include vascular and metabolic risk factors and disorders, lifestyle-related factors, medications and psychosocial factors. It is important to consider that for some modifiable factors the association with the incidence of dementia and AD in late life largely depends on the age of exposure, which thus defines specific “windows of opportunity” for prevention. This is the case for hypertension, obesity and hypercholesterolaemia: when occurring during middle age (<65 years), they represent risk factors for late-life dementia and AD. Among older adults, cardiovascular diseases (CVDs) and dementia are highly prevalent, and often hypertension and dementia as well as hyperlipidaemia and dementia exist simultaneously [96]. In 2019, Lennon et al. [97] found in their review of observational studies, midlife systolic hypertension above 160 mmHg was linked with an up to 25% increased risk of AD, representing 5% of all AD cases worldwide [98]. A recent meta-analysis of prospective cohort studies with median follow-ups across cohorts of 7–22 years, indicated that among people with high blood pressure, the use of antihypertensive medications was associated with a reduced risk of developing dementia (HR 0.88, 95% CI 0.79–0.98) and AD (HR 0.84, 95% CI: 0.73–0.97) compared to those who did not use those medications [99]. Additionally, previous studies have shown, serum cholesterol above 6.5mmol/L is known to be linked with an increased risk of 2.1 to develop AD [100]. However, in individuals aged over 75, reduced levels of blood pressure, body mass index (BMI), and total cholesterol have been linked to an increased risk of dementia and Alzheimer’s disease. This phenomenon, defined as “reverse causality”, is likely due to the fact that blood pressure, cholesterol, and BMI, often decrease in the early, asymptomatic stages of dementia/AD, probably also as a consequence of the disease process.

Other factors linked to metabolic and vascular health include diabetes mellitus [83,101,102]. Similar to hypertension, systematic reviews have shown that diabetes mellitus, due to increasing inflammation and oxidative stress on the brain [103], in mid- and late life is also associated with both AD and vascular dementia. This suggests that early glycaemic control, perhaps in the prediabetic stage, might be a promising therapeutic target for the prevention of cognitive decline [104,105].

In the continuum of later life cognitive decline that often leads to a high prevalence of dementia, cognitive reserve plays a crucial role [87], which can be mitigated through lifelong participation in diverse activities to delay the onset of dementia [106,107]. According to the concept of cognitive reserve, innate intelligence or life experiences, such as educational and occupational accomplishments, may offer a reserve in the form of a set of skills or repertoires that facilitate some individuals to cope with advancing pathology of AD better than others [108]. The current body of research indicates that education increases the basal level of cognition [109], thus, the threshold for expressing dementia symptoms will be reached later than in counterparts with lower initial cognitive levels [110,111]. The Bronx ageing study have shown that extensive participation in cognitive leisure activities is associated with a decreased risk of amnestic MCI in community dwellers [112], whereas the Kungsholmen Study has also demonstrated that engaging in daily mental activities is linked to a reduced risk (RR 0.59) of developing all-cause dementia [113,114]. Moreover, a previous study based on a novel volume-based PET imaging approach investigated that patients with higher levels of education, tau pathology is less paralleled by regional and remote neuronal dysfunction. The data suggested that early lifetime factors such as level of education support resilience mechanisms that ameliorate AD-related effects later in life [115].

Another crucial component contributing to good cognitive performance, enhancing cognitive reserve and recognised as an accepted protective factor [4], is socialisation. Several studies and meta-analyses have shown the positive impact of social contact and engagement on reducing the risk of dementia [116,117]. Another interesting factor is the potential for reverse causality, with dementia leading to social isolation and withdrawal from social interactions due to the presence of prodromal and subclinical signs and symptoms, might be present even a decade prior to its clinical onset [118,119]. These principles are grounded in the "use it or lose it" concept and include their role as a part of a healthy lifestyle, which involves engaging in cognitively stimulating activities according to individual interests, abilities, and education, and for individuals with dementia, prescribing activities to reduce passive behaviours and promote increased involvement in both cognitive and physical activities
[120].

No definitive treatments for dementia are present to this day, thus, epidemiological research plays a crucial role in identifying and focusing on modifiable risk factors, such as physical

activity [121]. A healthy lifestyle throughout the entire lifespan including physical activity, has been suggested to reduce the pathophysiology of dementia [87]. Since the early 1990s, research has indicated that regular physical activity represents one of the most important modifiable health factors and may help to delay the onset of dementia by supporting sustained cerebral blood flow [122]. Among all modifiable risk factors, physical inactivity exhibits the highest population-attributable risk (PAR) for Alzheimer's disease, with estimated proportions of 20.3% in Europe, 21.0% in the USA, and 21.8% in the United Kingdom) [124]. A randomised controlled trial (RCT) involving 138 adults aged 50 years and older who experienced subjective memory impairment, demonstrated that engaging in a six-month physical activity programme resulted in a slight improvement in cognitive function over an 18month follow-up period [124]. Moreover, aerobic exercise is associated with an increase in brain-derived neurotrophic factor (BDNF), a factor known to promote neuronal cell growth and maintain neurons in an optimal state [125].

Previous studies have demonstrated that aerobic exercise leads to a decrease in antiinflammatory biomarkers such as Tumour Necrosis Factor Alpha (TNF-α), C-reactive Protein (CRP), and various interleukins - markers that have been shown to be present at elevated serum levels in individuals with dementia [83]. Another study has shown that during physical activity, the messenger substance irisin was released from muscles through the gap of the transmembrane protein Fibronectin Type III Domain Containing 5 (FNDC5) and reached the human brain through the bloodstream. AD patients have been shown to have decreased levels of FNDC5/irisin in the hippocampus and cerebrospinal fluid (CSF). An increase in the FNDC5/irisin concentration have led to an improvement in neurogenesis and synaptic plasticity. This occurs as a reaction to injuries of the neuronal tissue, in contrast, it is a natural process that enables the organism to react to and adapt to changes in its environment [126].

Recent findings in microbiome research indicate that physical exercise may have a modulatory effect on microbial composition, and consequently on neurodegenerative processes [127]. During physical exercise, increased cerebral blood flow might promote the degradation of hyperphosphorylated tau proteins and ß-amyloid plaques [128].

In individuals living with dementia, physical activity and exercise interventions may have additional benefits, including reducing the risk of disability, falls, and neuropsychiatric symptoms [129]. In a prospective study of community-living older persons, it was shown that physical activity/exercise may decrease the risk of falls by approximately 31% (204 falls every 1000 people affected by dementia treated with this intervention), and considering that falls are significant contributors to disability, it is reasonable to propose that the positive impact of physical activity/exercise on reducing the risk of falls could subsequently enhance daily living activities [130].

In the context of physical activity and exercise, there are currently no dementia-specific guidelines for the prevention or management of dementia or MCI. Although observational studies consistently suggest a positive association between physical activity and cognitive functioning, interventional evidence remains limited and conclusive findings are still pending. Nonetheless, regular physical activity is considered a central pillar in promoting healthy cognitive ageing and can be recommended to both cognitively healthy adults and older individuals, regardless of the presence of cognitive impairment. Individuals with MCI are encouraged to engage in a moderate but regular, variable exercise programme, with a minimum of 30 minutes of activity, three times a week, incorporating a mix of walking, challenging aerobic exercises, and participation in group sports [4, 87].

The Lancet Commission on dementia prevention, intervention, and care has added new modifiable risk factors for dementia, such as excessive alcohol consumption and head injuries (TBI), to its agenda. Excessive and long-term alcohol consumption in midlife appears to cause neurotoxicity and neuroinflammation, and also affects the brain indirectly by promoting nutritional deficiency (thiamine) [4,111]. The UK Whitehall study, with 23-year follow-up, included 9,087 participants aged 35–55 years at baseline [132]. Drinking more than 21 units per week and long-term abstinence were both linked to a 17% (95% CI 4–32 and 13–23 respectively) increase in dementia, compared to drinking less than 14 units. Additionally, the alcohol consumption of more than 14 units was correlated with right-sided hippocampal atrophy on MRI [133].

TBI are usually caused by motorcycle, car, and bicycle injuries; military exposures; horse riding, boxing, and other recreational sports; firearms; and falls [134]. A nationwide Danish cohort study of nearly 3 million participants aged 50 years or older, followed for a mean of 10 years, found an increased risk of dementia (HR 1·2, 95% CI 1·2–1·3) and AD risk (1·2, 1·1– 1·2) [135]. Furthermore, at advanced age, tobacco use is another modifiable risk factor not only for CVDs but also for dementia. Taking into account the global prevalence of smokers (around 30%), it is estimated that roughly 14% (equivalent to around 4.7 million cases) of all AD cases worldwide are attributable to smoking [98]. Among 50,000 men aged over 60 years, who had stopped smoking for more than 4 years, there was a significant reduction in the risk of dementia over the following 8 years compared to those who continued smoking (HR 0.9; 95% CI 0.7–1.0) [136].

Evidence from previous research indicates that among middle-aged adults (aged 45 to 65 years), hearing loss represents the most influential of all known modifiable risk factors, with estimates suggesting that up to 8 % of dementia cases could be prevented by addressing it [4]. A cross-sectional study involving 6,451 individuals, designed to represent the U.S. population with an average age of 59.4 years, found a decline in cognitive function with every 10 dB reduction in hearing. This cognitive decline persisted even below the clinical threshold,

highlighting a significant association between subclinical levels of hearing impairment (below 25 dB) and lower cognitive function [137]. Secondary effects, such as depression often followed by social isolation, have been seen especially with hearing loss being present at the same time [138]. Numerous studies have reported that individuals with a history of depression are more prone to develop AD in older life [139], contributing to the classification of depression as a risk factor for AD in general [140].

Another pillar for healthy cognitive ageing is sleep. Numerous studies have shown that sleep has considerable importance for the functioning of the human brain. During sleep, the nervous system is cleansed of toxic substances and waste products, especially those associated with dementia [141]. The most common sleep-related disorders are exogenously triggered by poor sleep hygiene or a lack of bedtime [22]. Recent studies show that sleep deprivation can increase overnight amyloid-ß production by up to 25–30%, making it a risk factor for cognitive function decline [142,143]. Moreover, a systematic review and metaanalysis found that sleep disturbances, including short and long sleep duration, poor sleep quality, circadian rhythm abnormality, insomnia, and OSA, were all linked to a higher risk of all-cause dementia, Relative Risk (RR 1·2; 95% CI 1·1–1·3) [144] and clinically diagnosed AD (1·6, 1·3–1·9) compared with no sleep disturbance [145]. According to the latest findings, the optimal sleep length is determined between the 20th and 30th year of life, lies between 4 and 10 hours and does not change in the course of life–even in old age [146]. Thus, the diagnosis and treatment of sleep-wake disorders is an important component of the prevention of cognitive decline.

The Lancet Commission on dementia in 2024, did not include diet in its list of modifiable risk factors. Instead, dietary habits have been viewed as a single protective element within broader lifestyle-related considerations. However, diet is a multidimensional exposure that encompasses various healthy and unhealthy elements, provided by food and beverages, often within specific habits, and sometimes as part of a multimodal constellation involving education, socioeconomic status, dietary patterns, physical activity, other lifestyle factors, and environmental factors [147]. For dementia risk control, similar to maintenance of healthy ageing and prevention of age-related chronic diseases, diet plays a crucial role. Cellular protection against oxidative toxicity is supported by bioactive compounds like antioxidants, predominantly found in fruits and vegetables [148]. For healthy cognitive ageing, a healthy lifestyle with avoidance of nutrient deficiency and restrictive diet in young adulthood is essential [149]. Early childhood nutrition already plays an essential role in brain development and forms the basis for good cognitive function in the future [149].

A reduction of food intake, eating behaviour disturbances, and loss of body weight are particularly significant problems in individuals diagnosed with AD. First symptoms of malnutrition should be recognised and corrected as early as possible, as malnutrition has been shown to be linked with a more rapid worsening of AD [150]. A healthy diet in general, and the

MeDi in particular, have recently been shown to have a beneficial impact on the risk for and mortality from AD [151,152,153,154]. Moreover, evidence from a review of 34 studies focusing on antioxidants, dietary restriction, and the Mediterranean diet (MeDi) highlights the considerable potential of nutritional approaches to modulate the onset and progression of dementia and Alzheimer's disease [155].

As described above, since dementia cannot be cured, there is increasing consensus that identifying and implementing prevention strategies to prevent or slow down the progression of dementia is essential. If effective prevention strategies could be identified and standardised, biomarkers [156], as well as the general [157] and cognitive [158] assessment of preclinical dementia pathology, could potentially be incorporated among other screening tools in the field of preventive medicine. By influencing lifestyle in various ways, an impact on prevalence and incidence decrease might be achieved in the future.

3.4. Nutritional cognitive neuroscience of ageing

3.4.1. The ageing brain

The ageing process, including brain ageing, is multifactorial and heterogeneous, making it challenging to isolate specific mechanisms. Ageing itself is characterised by the gradual accumulation of cellular and molecular damage throughout the lifespan, and is closely linked to physical decline and an increased risk of developing disease, including neurodegenerative disorders [159]. It is crucial to acknowledge a key yet understated fact that age is the major risk factor for age-related cognitive disorders, consisting of dementia and that the pathophysiology of ageing with its multiple age-related changes strikingly resembles the characteristics of the ageing brain, through a continuum from normal cognitive function to dementia [160]. The pathophysiology of age-related cognitive impairment and dementia is multifactorial, highly complex and ranges from traditional amyloid-β- and τ-hypotheses to genetic factors, and a lifelong exposure to the imbalance between the multitude of vascular and lifestyle protective and risk factors [23]. In other words, the primary age-related neurodegenerative characteristics including structural, cellular, molecular, biochemical, vascular changes reflect intrinsic and extrinsic features of the ageing process itself and are associated with cognition outcomes [27]. Across the biomolecular to phenotypical to clinical manifestations, all age-related alterations contribute to memory loss, impairment of other cognitive domains and neurological and neuropsychiatric systems. For the same reason, motoric alterations, posture, balance and gait disorders, sleep disturbances, sensory decrements, personality changes and mood disorders are among the features associated with dementia [162].

Neurodegenerative diseases share a common predisposing factor: the brain ageing. At the molecular level, this process is reflected in increased cellular ageing of neurons and microglia. It is accompanied by enhanced apoptosis, accumulation of misfolded proteins, mitochondrial dysfunction with elevated production of reactive oxygen species, oxidative damage to proteins and lipids, and a progressive accumulation of DNA damage [163]. The brain is particularly susceptible to oxidative stress, yet it exhibits comparatively low levels of endogenous antioxidant defence mechanisms. As a consequence, extracellular accumulation of β-amyloid (Aβ) plaques and the formation of intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau occur—both of which are the major hallmarks of the Alzheimer's brain and play a key role in its pathogenesis. [23,164,165].

Due to the brain´s high energy demands, supplied by the anaerobic oxidation of glucose, with ageing there is a decrease in neuronal glucose transporters, and as a result, a decrease in glucose uptake, which is associated with cognitive decline [23]. Moreover, mitochondrial oxidative phosphorylation (OXPHOS) function becomes progressively impaired, accompanied by an increased generation of reactive oxygen species (ROS). This initiates a self-perpetuating cycle in which mitochondrial DNA sustains damage, further compromising OXPHOS efficiency [167]. Increased neuroinflammation is a feature of brain ageing, whilst misfolded and aggregated proteins bind to microglia Toll-like receptors and Cluster of differentiation 4 (CD4), triggering the inflammatory response. If it is uncontrolled and persistent it could be destructive due to the release of ROS and Reactive nitrogen species (RNS) [168]. Within this complexity, the central nervous system (CNS)—a tissue that is highly dependent on oxygen—is particularly sensitive to changes in oxygen levels and to the elevated production of derivatives of molecular oxygen (which are otherwise normally formed as an attribute of aerobic life), ROS.

3.4.2. Oxidative distress and eustress in brain

Among the mechanisms considered to play a key role in the transition from normal brain ageing to cognitive impairment and ultimately to Alzheimer's disease and other forms of dementia is the increased production of ROS, RNS, and other free radicals, which has repeatedly been described as a central factor. [23,169,32]. The CNS is among the most oxygen-sensitive tissues in the body [170], and exhibits a pronounced vulnerability to fluctuations in oxygen availability. Such instability promotes the excessive formation of molecular oxygen derivatives, particularly endogenous ROS. The term 'oxidative distress' refers to a pathological condition characterised by elevated levels of ROS, which can induce molecular damage. In contrast, 'oxidative eustress' describes the physiological balance of ROS, where they play a regulatory role in redox signalling, including specific posttranslational modifications [171].

An imbalance in cellular redox homeostasis—particularly in the context of sustained oxidative stress—is regarded as a key hallmark of the ageing process. It contributes substantially to the pathogenesis of neurodegenerative disorders, including chronic degenerative conditions such as AD, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis [170]. Damage to the CNS, such as the accumulation of protein aggregates associated with neurodegenerative disorders, leads to the production of oxidants, involving both neurons and microglia, which are known to be the main phagocytes in the brain that serve as neuronsupporting cells. Generally, this response is meant to be protective by clearing debris and supporting neuronal survival. However, in specific cases, microglia become overactivated and overproduce ROS and RNS, as a result inhibiting neuronal and oligodendroglial survival [172]. Furthermore, locally increased levels of ROS can precipitate neuronal mitochondrial dysfunction, with neuronal mitochondria shown to be particularly susceptible to oxidative damage, by deterioration membrane proteins and may cause adverse mutations in mitochondrial DNA [173,174]. The endpoint of this cascade is neuroinflammation and neuronal dysfunction as seen in AD [175,176,177].

Neuronal cells within the brain have been shown to exhibit particular vulnerability to oxidative injury, owing to their elevated oxygen consumption, relatively limited antioxidant defences [178], and the abundance of polyunsaturated fatty acids (PUFAs) within their membranes. These lipids, characterised by multiple double bonds, render the membrane especially susceptible to free radical attack, as reactive oxygen and nitrogen species (RONS) readily abstract hydrogen atoms [179]. The overproduction of ROS and RNS in brain cells of ROS and RNS may trigger lipid peroxidation [180], leading to diminished membrane fluidity and increased permeability. This, in turn, facilitates uncontrolled influxes of ions such as K^+ and Ca^{2+}, potentially disrupting membrane-bound proteins, enzymes, and receptor functions [181].

There are a multitude of antioxidant defensive mechanisms against ROS and RNS, so the reduction of oxidative stress and the protection of mitochondria is an important objective in the prevention and treatment of dementia, particularly in AD [182]. Antioxidant defence systems can be categorised into two functional groups: enzymatic and non-enzymatic components. The enzymatic group includes key enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR). SOD plays a pivotal role in neutralising ROS by converting superoxide anions into hydrogen peroxide and molecular oxygen [183]. CAT subsequently catalyses the decomposition of hydrogen peroxide into water and oxygen [184]. The non-enzymatic group encompasses molecules such as glutathione (GSH), which is present in high concentrations in neural tissue, as well as thioredoxin (Trx), vitamins A, C and E, selenium, retinoic acid, carotenoids, and flavonoids. GSH reacts with ROS to form glutathione disulphide (GSSG) and is regenerated within an antioxidant cycle involving GPx and GR [185]. Collectively, these systems form a vital protective network against oxidative stress [186]. However, when antioxidant defences are insufficient and levels of

polyunsaturated lipids are elevated, the accumulation of biomolecules damaged by ROS and RNS may occur [187].

The antioxidant system interrupts the proliferation of free radicals, prevents the formation of free radicals, cleans damaged molecules, repairs oxidative damage, and prevents mutations through different mechanisms [188]. Antioxidants play an essential role in eliminating the species that initiate the peroxidation, breaking the autoxidative chain reaction, extinguishing superoxide ions, and preventing the formation of peroxides [189]. Moreover, besides antioxidant enzymes produced by the body, low molecular weight antioxidants, such as minerals, vitamins, carotenoids, cofactors, glutathione, and polyphenols are vital for antioxidative defence mechanisms of cells and organisms [190]. While Ascorbic acid (AA) and tocopherol (vitamin E) cannot be synthesised by a human [191], there are several molecules that are produced in the human body and possess an antioxidant effect including glutathione, lipoic acid, uric acid, taurine, keto acids, melatonin, coenzyme Q, and melanins [192].

The risk of developing neurodegenerative diseases can be influenced by preventive approaches targeting vascular health and modifiable lifestyle factors, such as regular physical activity and a balanced diet. Evidence suggests that improving lifestyle and managing vascular risk parameters may decelerate cognitive decline, in part by reducing the formation of ROS and RNS [193,194].

To conclude, oxidative stress is widely acknowledged as a key contributing factor in both the onset and progression of neurodegenerative disorders. An imbalance in redox homeostasis, marked by the excessive accumulation of reactive oxygen and nitrogen species, plays a decisive role in neuronal dysfunction and cellular damage. Within this framework, a wellbalanced diet enriched with natural antioxidants may represent an effective preventive approach. By strengthening endogenous antioxidant defence systems, such nutritional strategies could offer protection against oxidative injury and help preserve cognitive function throughout the ageing process [195,196,197,198].

3.4.3. Micronutrients profile in cognitive impairment

As neurodegenerative changes unfold along a continuum from normal brain ageing to dementia, the field of nutritional cognitive neuroscience has emerged to explore the influence of dietary factors and micronutrient profiles on cognitive frailty in later life [162]. Increasing evidence highlights the relevance of a sufficient and well-balanced dietary intake as a modifiable factor in the context of age-related cognitive decline [199]. The brain depends on a proper amount of key nutrients to sustain neuronal integrity and neurotransmitter synthesis. Both macro- and micronutrients provide essential substrates and precursors that must be

obtained through diet. Among these, fruits and vegetables represent an important dietary source of vitamins and antioxidant micronutrients, which contribute to the preservation of cognitive function in later life [23].

Current data underscore the substantial contribution of inadequate dietary habits to morbidity and mortality across Europe [200,201]. According to the European Nutrition and Health Report 2021, poor nutrition has emerged as a principal cause of death, with associated fatalities rising by 15% since 2010—outpacing population growth and now accounting for over 12 million deaths annually from non-communicable diseases, representing 26% of all adult mortality. On a global level, dietary patterns remain far from optimal, with little measurable improvement observed over the past decade [202]. Consumption of fruits and vegetables continues to fall markedly below the recommended threshold of five daily portions, by approximately 60% and 40% respectively, while the intake of legumes and nuts lags by more than two-thirds relative to dietary guidelines.
These trends are particularly relevant in the context of cognitive ageing, as an insufficient dietary supply of essential micronutrients may compromise neurocognitive resilience and accelerate functional decline [202].

A multitude of dietary components and supplements with potential antioxidant, antiinflammatory, and vasodilating actions have been investigated in numerous studies on their impact on cognitive decline. The carotenoids analysed in the present study have been found to be efficient lipophilic antioxidants in living entity [203] with an impressive impact on health in relation to several age-related diseases, cognitive and physical performance [204]. Moreover, the implication of carotenoids on the pathophysiology of AD and dementia has been extensively researched in several studies [205]. Tissue carotenoids are naturally occurring lipophilic compounds, function as robust biomarkers in different organisms, such as plants, animals, and microorganisms. Human beings and animals acquire carotenoids with the diet since they cannot synthesise them. In human organisms around 40 different carotenoids can be found, with α- and β-carotene, β-cryptoxanthin, lycopene, lutein, zeaxanthin the most prominent [162]. Moreover, it must be acknowledged that factors such as carotenoid metabolism, distribution, and bioavailability—as well as dietary intake—are subject to considerable interindividual variability. This variability is influenced by a combination of host-related determinants, including chronological age, lifestyle behaviours, underlying health conditions, genetic predispositions, and biological sex [206]. These factors together determine an individual´s carotenoid pattern in the blood and tissue, and impact the production of carotenoid metabolites and their distribution [162]. Understanding the biochemistry of carotenoids is crucial for comprehending their beneficial effects, thus their special role in nutritional cognitive neuroscience. Characterised as highly lipophilic molecules which reside intracellularly to protect the membrane from oxidative stress [207], they reduce reactive byproducts such as ROS thus functioning as antioxidants. The polarity of carotenoids play a

decisive role in determining their distribution within human tissues. Notably, xanthophylls constitute approximately 66–77% of total carotenoids detected in the frontal and occipital regions of the brain, despite representing less than 40% of total carotenoids in most peripheral tissues and plasma [204]. Compelling evidence indicates that lutein and its structural isomer zeaxanthin accumulate progressively within neural tissues over the lifespan. These carotenoids are able to cross the blood–retina barrier and and integrate into the macular pigment [208] where they contribute to the protection against ageassociated eye diseases [209]. Previous studies have shown that lutein is the most prevalent carotenoid in human brain tissue [210,211,212]. The presence of these biochemical characteristics strongly suggests that these micronutrients play a pivotal role in nervous tissue´s physiology and functioning. Lutein is the primary carotenoid found in brain tissue despite not being the major carotenoid in matched serum indicating the prioritised uptake into brain tissue [213]. Previous studies have also observed a significant correlation between lutein and zeaxanthin in macula and their levels in matched brain tissue [214], hence macular pigment can be used as a biomarker in brain tissue. A significant correlation has been established between macular pigment optical density and cognitive performance, underscoring the localisation of lutein and zeaxanthin within the central retinal region [215,216]. In a population-based study that explored the brain tissue of decedents, associations were identified between lutein levels and a diverse set of cognitive measures [217], similar to our study, including learning, executive functions, memory and language. A large body of literature has examined these functions were discovered to be particularly connected to carotenoid levels within specific regions of the brain.

In the Healthy Ageing in Neighbourhoods of Diversity across the Life Span (HANDLS) study, a statistically significant association was observed between vitamin E levels and verbal memory performance ($p = 0.002$). Lycopene, a carotenoid compound, was identified as a key contributing factor to this relationship. [218]. Moreover, the Rush Memory and Ageing Project further identified a negative correlation between overall brain pathology and the presence of the carotenoids lutein–zeaxanthin and lycopene, suggesting their potential neuroprotective function [219]. These findings match the results of a previous study of Polidori et al. and Dias et. al, indicating that in AD patients with vascular comorbidities, the levels of lutein, lycopene, and zeaxanthin were significantly lower in comparison to those observed in healthy subjects [220, 221].

In our study, a significant correlation was found between plasma concentrations of several lipophilic micronutrients and the International Shopping List Task (ISLT) of the CogState Battery, assessing verbal learning and memory [222], and the Timed Up and Go (TUG) test for assessing physical activity and mobility [223]. As previously shown by Nelles et al. and Stoddart et al., a significant correlation between cognitive measures and endothelial function [224,32], seen as a significant contributor of cognitive impairment [32], as well as between

measures of global cognition and plasma concentrations of lipophilic micronutrients are in strong agreement with previous reports [204, 221, 224,226,227, 228].

Furthermore, it is important to acknowledge that various other dietary constituents may exert a considerable influence on cognitive performance. Crocin has been shown to protect neurons against neurodegenerative processes, by enhancing the antioxidant defense system of the brain, reduction of oxidative stress and prevention of the development of neurodegenerative diseases [229,230]. A high intake of AA may serve as a protection for neurons against neurodegenerative diseases by readjusting the redox state [231]. Moreover, emerging evidence suggests that diets rich in omega-3 fatty acids may exert neuroprotective effects against oxidative stress-induced neurodegeneration. As such, omega-3 supplementation could represent a promising element within multidomain intervention strategies, including nutritional approaches [232].

Research indicates that elevated homocysteine levels are commonly observed in individuals with vascular dementia and AD. Both epidemiological and clinical studies suggest that maintaining low homocysteine levels through sufficient intake of vitamins B6, B9 and B12 may reduce the risk of AD [233]. Nevertheless, multiple prospective studies have associated low levels of vitamin D in elderly patients with an increased risk of cognitive impairment [20, 243, 244].

Furthermore, studies have shown that green tea consumption is a significant protective factor for cognitive health, linked to antioxidants such as Epigallocatechin-3-gallate (EGCG), Ltheanine, and caffeine [246]. One cup of tea per day is associated with a 6% reduction in the risk of cognitive deficits [247]. When considering the design of such studies, the role of probiotic bacteria warrants careful attention, given their well-documented anti-inflammatory effects on the gastrointestinal system and other physiological benefits. Probiotics serve as a protective barrier by preventing the translocation of pro-inflammatory agents into the bloodstream—an effect that may be relevant in the context of neurodegenerative conditions. Conversely, in instances of dysbiosis, these inflammatory agents may cross the blood–brain barrier and potentially contribute to the pathogenesis of AD [204]. In light of recent investigations, together with our study, particular carotenoids and other micronutrients play an exceptional role in cognitive performance together with physical activity, advocating for a focused exploration of their application in cognitive health optimisation and therapeutic innovation, in forms of holistic lifestyle changes that include both physical as well as dietary interventions.

3.5. Relevante Fragestellungen im aktuellen Kontext

Das Altern ist ein komplexer Prozess, der zahlreiche biologische, psychologische und soziale Veränderungen umfasst. Das Verständnis der Faktoren, die den kognitiven und physischen Abbau beeinflussen, ist entscheidend für die Entwicklung wirksamer Präventionsstrategien. Unser Paper dient als wertvolle Ressource zur Erforschung des Alterungsprozesses, insbesondere im Hinblick darauf, wie Lebensstilfaktoren, wie zum Beispiel Ernährung, die kognitive und physische Fitness bei älteren Erwachsenen mit leichter kognitiver Beeinträchtigung (MCI) beeinflussen können.

Um diese Wissenslücke zu schließen, untersuchte die NeuroExercise-Studie – eine multizentrische, randomisierte kontrollierte Studie, die in drei europäischen Ländern (Deutschland, Niederlande und Irland) durchgeführt wurde – diese Zusammenhänge. Die Studie bewertete die Auswirkungen eines 12-monatigen strukturierten Bewegungsprogramms auf die Progression der leichten kognitiven Beeinträchtigung (MCI) und konzentrierte sich dabei auf kognitive und physische Ergebnisse, die durch verschiedene spezifische Tests gemessen wurden.
Unser Paper präsentiert eine Teilstudie aus der NeuroExercise-Studie, die nur deutsche Teilnehmer einschließt, die zusätzlich zur Intervention eine Blutabnahme vor und nach dem Interventionszeitraum sowie andere Messungen durchliefen. Ziel war es, die Zusammenhänge zwischen den Plasmaspiegeln von Carotinoiden und Tocopherolen – Biomarker, die mit Ernährung und antioxidativem Schutz in Verbindung stehen – und Indikatoren für physische und kognitive Leistungsfähigkeit bei Personen mit MCI, die ein strukturiertes Bewegungsprogramm befolgten, zu untersuchen.

Die Ergebnisse dieser Teilstudie bilden die Grundlage unserer Dissertation. In den folgenden Kapiteln werden weitere Studien zur kognitiven Funktion und zum Mikronährstoffstatus diskutiert, um ein umfassendes Verständnis des Themas zu bieten.

3.6. Current Fundamental Questions

Ageing is a complex process that involves numerous biological, psychological, and social changes. Understanding the factors that influence cognitive and physical decline is crucial for developing effective preventive strategies. This paper serves as a valuable resource for exploring the ageing process, particularly by focusing on how lifestyle factors such as nutrition, can influence cognitive and physical fitness in older adults with MCI.

To address this gap in knowledge, the NeuroExercise study—a multicentre randomised controlled trial conducted in three European countries (Germany, Netherlands, and Ireland)—investigated these relationships. The study assessed the effects of a 12-month structured exercise programme on the progression of MCI, focusing on cognitive and physical outcomes measured through various specific tests.

This paper presents a sub-study from the NeuroExercise study, including only German participants who underwent additional blood sampling before and after the intervention alongside other measurements. The objective was to investigate the relationship between plasma levels of carotenoids and tocopherols—nutritional biomarkers linked to antioxidant defence—and measures of cognitive and physical performance in individuals with MCI undergoing a structured exercise intervention.

The results of this sub-study form the basis of this paper. In the following chapters, other studies on cognitive function and micronutrient status are also discussed to provide a comprehensive understanding of the topic.

3.7. Aim of the study

The primary aim of this study was to investigate the relationship between plasma levels of lipophilic micronutrients, particularly carotenoids and tocopherols, and their association with cognitive and physical performance in individuals with MCI. The rationale for this focus is rooted in the growing body of evidence suggesting a potential link between dietary nutrients and the preservation of cognitive function, a subject of increasing relevance given the ageing global population and the consequent rise in age-related cognitive disorders.

The main interest was to compare the plasma micronutrient levels observed in individuals with MCI against established data from healthy cohorts. This comparative approach is crucial for identifying potential differences that may suggest a distinct nutritional profile associated with cognitive impairment. By examining these disparities, the study endeavours to highlight the unique nutritional needs of individuals with MCI, which could be instrumental in developing targeted dietary strategies for this group.

The study also aimed to identify the direct associations of micronutrient levels with cognitive and physical performance, independent of broader dietary patterns, such as fruit and vegetable intake. This objective was pursued to determine whether the micronutrients themselves might be the contributing factors to cognitive health, rather than being indicators of a generally healthy diet. This distinction is vital for understanding the potential of specific nutrients to serve as therapeutic agents in cognitive decline.

Furthermore, the results garnered from the present study may provide information for the development of future clinical trials that may explore the efficacy of micronutrient supplementation in preventing or slowing down cognitive decline. Such interventional studies are critical for progressing beyond correlational results to establish causality and practical applications to prevent or slow down cognitive impairment.

Through these objectives, the study not only aimed to contribute to the existing body of knowledge on the role of diet in cognitive health but also to pave the way for practical healthcare interventions that could have a meaningful impact on the lives of individuals at risk of or experiencing cognitive decline.

The pursuit of these objectives aims to deepen understanding of nutritional cognitive neuroscience, with a long-term view towards developing dietary recommendations and interventions that could reduce the risk or progression of cognitive impairment in older adults. By focusing on a population with MCI, the study targets a critical stage where intervention may be particularly beneficial, potentially providing information for developing strategies to maintain cognitive robustness and promote healthy ageing.

3.8. Research gap

While the number of cognitively fit and independent older adults is increasing, there is also a significant proportion of older individuals who can no longer manage daily life independently due to multiple chronic conditions. Age-associated cognitive impairments, particularly dementia, are a global concern affecting over 55 million people worldwide [20]. This raises the question of what factors enable some individuals to preserve their cognitive abilities into old age, and how we can therapeutically apply these findings.

The ageing process, with all its associated positive and negative effects, is influenced by a multidimensional set of variables. Previous studies have shown that, by living a preventive lifestyle, it is possible to slow down or even prevent cognitive decline during ageing. However, there is still a lack of specific evidence regarding the long-term reciprocal relationships among these various factors.

To fill this knowledge gap, a multicentre randomised controlled trial called the NeuroExercise study was conducted across three European countries (Germany, Netherlands, Ireland). Our study aimed to address this gap by examining the potential impact of lipophilic micronutrients on cognitive health and physical fitness, thereby contributing to the development of new preventive lifestyle strategies.

Despite the growing body of research highlighting the importance of modifiable risk factors in dementia prevention, there remains a critical gap in understanding how specific lipophilic

micronutrients influence cognitive and physical health. Current guidelines and studies emphasise general lifestyle modifications, such as diet and exercise, but often lack specificity regarding which nutrients are most beneficial and how they interact with cognitive functions

Our study underscores the necessity for personalised nutritional strategies. While general dietary guidelines exist, there is a pressing need for more targeted recommendations that consider individual variations in diet, genetic factors, and baseline nutritional status. Our findings highlight the need for a multidimensional and personalised prevention strategy tailored to individual risk profiles. By providing empirical data on the correlations between specific micronutrients and cognitive health, this research lays the groundwork for developing tailored nutritional interventions that can more effectively prevent or mitigate cognitive decline.

While our present study has identified associations between specific plasma carotenoid levels and cognitive as well as physical performance in individuals with MCI, it has also highlighted several research gaps that warrants further investigation. The correlational nature of this study leaves the causal mechanisms underlying these associations unclear. Therefore, a significant research gap exists in determining the causal pathways through which micronutrients might influence cognitive and physical performance. Prospective longitudinal studies or randomised controlled trials are needed to establish causality and understand the underlying biological mechanisms.

Previous research has established the role of oxidative stress and antioxidant defence mechanisms in cognitive decline, yet there is insufficient evidence on the specific impacts of individual micronutrients. This study is pioneering in its approach to linking specific biomarkers of nutrition and antioxidant defence directly with performance measures.

In summary, our study fills a significant research gap by elucidating the role of specific lipophilic micronutrients in cognitive and physical health, offering new insights that could inform the development of personalised and more effective preventive strategies against cognitive impairments in the ageing population. Furthermore, the research gaps identified by this study present opportunities for further exploration into the complex interaction between diet, physical activity, micronutrient status, and brain health. Addressing these gaps is crucial for developing targeted nutritional interventions aimed at preserving cognitive function and preventing cognitive decline.

The insights from this study can also help develop public health policies and preventive measures that reach broader populations and promote healthy ageing. By recognising the importance of individual differences and the need for tailored approaches, we can develop a more comprehensive and inclusive strategy to combat cognitive impairments in old age.

nutrients

MDPI

Article

Associations of Lipophilic Micronutrients with Physical and Cognitive Fitness in Persons with Mild Cognitive Impairment

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Received: 7 February 2019; Accepted: 9 April 2019; Published: 22 April 2019

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Abstract: Age-associated cognitive impairment in general and dementia in particular are a global concern. Preventive lifestyle strategies are highly used but there is a lack of information on the reciprocal relationships between nutrition biomarkers and measures of both cognitive and physical performance. To fill this gap of knowledge, the relationship between plasma levels of the robust nutrition- and antioxidant defense-related biomarkers carotenoid and tocopherols and both indicators of cognitive and physical performance was investigated in a group of persons with mild cognitive impairment participating in the NeuroExercise Study at the German Sport University in Cologne, Germany. In 56 participants with full dataset, significant correlations independently of fruit and vegetable intake were found between plasma levels of β-cryptoxanthin and Timed Up&Go test ($p < 0.05$), γ-tocopherol and number of daily steps ($p < 0.01$), as well as between four out of six measured carotenoids—lutein; zeaxanthin; β-cryptoxanthin and β-carotene—and the computerized CogState International Shopping List subtest ($p < 0.01$). In light of the increasing attention towards the nutritional cognitive neuroscience of carotenoids, computerized measures of cognitive performance might be further implemented in future studies investigating the effects of lifestyle interventions against cognitive and physical impairment.

Keywords: cognitive performance; physical activity; micronutrients; carotenoids; mild cognitive impairment; nutrition; neuropsychological tests

1. Introduction

Socioeconomic challenges associated with the ageing of the population demand concerted response worldwide as the increasing proportion of older people leads to changing needs in health and social care, with multi- and interdisciplinarity, networking and translational approaches moving to the forefront. Among the biggest medical challenges caused by chronic conditions in advanced age, cognitive impairment plays a major role [1,2]. Cognitive decline displays as diminished orientation or ability to remember, judge, understand and reason. It may be accompanied by a decrease in several other cognitive abilities and is extremely frequent in advanced age. For severe cognitive impairment, the term dementia (from the latin *de*, "out of", and *mens*, "mind") is commonly used. Cognitive decline and cognitive impairment with or without dementia are multifactorial syndromes rather than a single *one cause–one mechanism* disease.

To the main features of cognitive decline with and without dementia—multifactoriality, heterogeneity, poor diagnosis, increasing prevalence [1–3]—one adds causing major public health concern, i.e., that dementia is not curable. Therefore, attention is shifted towards the need of early diagnosing cognitive changes to slow down their progression. Age-related cognitive decline, subjective cognitive impairment (SCI) [4], and mild cognitive impairment (MCI) [5] are therefore object of a large body of investigations prompted at identifying the best possible preventive strategies. While the frantic, challenged search for effective antidementia drugs is ongoing, preliminary studies on the role of vascular- and lifestyle-related preventive strategies show that vascular risk control and lifestyle improvement are indeed able to slow down the progression of cognitive impairment [2,6,7]. Among lifestyle interventions, cognitive training programs, physical exercise interventions, and dietary strategies gained a great deal of attention recently (see present special issue). Several of these studies are based upon the evidence that oxidative stress, a critical pathophysiological mechanism in the onset and progression of cognitive impairment [8], can be substantially influenced by physical activity [9] and nutrition [10]. In particular, several biomarkers of oxidative stress and indicators of antioxidant micronutrient defense against free radicals have been shown to be associated with cognitive impairment with and without dementia [11]. Although the results of these studies are highly promising, the interactions between the different components of lifestyle across the course of cognitive impairment have not been clearly identified yet. This might be relevant to explain the conflicting results of lifestyle interventions including the multidomain ones [12] and to plan more personalized treatments in the future.

To fill this gap of knowledge, we investigated the relationship between robust nutrition- and antioxidant defense-related biomarkers including six carotenoids, two tocopherols and retinol, and indicators of both cognitive and physical performance in a group of persons with MCI participating in the NeuroExercise Study at the German Sport University in Cologne, Germany.

2. Participants and Methods

2.1. Participants

All participants were recruited through the NeuroExercise Project [13,14], a multi-centered randomized controlled trial of exercise therapy in persons with MCI according to Albert et al. [15] across three European countries [13]. 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. Participants were recruited through newspaper advertisements and all of them provided informed consent to the study procedures. Participants were included if the Montreal Cognitive Assessment (MoCA) [16] scored ranged between 18 and 26; if they had a stable medical condition for more than 6 months and stable medication for more than 3 months; adequate visual and auditory acuity to complete neuropsychological testing, electrocardiogram without significant abnormalities that might interfere with the study; physical ability sufficient to allow performance of endurance exercise training;

capacity to provide written and dated informed consent form, as well as having complete physical examination including a symptom-limited cardiopulmonary exercise test. To distinguish between amnestic and non-amnestic MCI, agreed education adjusted cut-offs of −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) were derived from the delayed recall portion of the age-adjusted delayed memory index of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [17] (Score of < 85) as previously described [13,14].

Exclusion criteria were diagnosis of Alzheimer's disease (AD) or other type of dementia, history of familial early-onset dementia; enrollment in any investigational drug study; history in the past 2 years of epileptic seizures; any major psychiatric disorder (a clinical diagnosis of major depressive disorder, bipolar or schizophrenia); past history or MRI evidence of brain damage, including significant trauma, stroke, hydrocephalus, mental retardation, or serious neurological disorder as well as carotid stent or severe stenosis; history of myocardial infarction within previous year, congestive heart failure (New York Heart Association Class II, III or IV); uncontrolled hypertension or hypotension (systolic blood pressure >200 mm Hg and/or diastolic blood pressure >110 mm Hg at rest); unstable cardiac, renal, lung, liver, or other severe chronic disease; type 2 diabetes mellitus with hypoglycemia in the last 3 months; significant history of alcoholism or drug abuse within last 10 years; engagement in moderate-intensity aerobic exercise training for more than 30 min, 3 times per week, during past 2 years; history of vitamin B12 deficiency or hypothyroidism (stable treatment for at least 3 months is allowed); and serious or non-healing wound, ulcer, or bone fracture [13].

After signing informed consent and passing the eligibility criteria, all participants underwent baseline assessment, including collection of history and lifestyle habits, neuropsychological testing, testing of general physical and cardiovascular performance. Participants were then randomly allocated to one of the three interventions (aerobic vs. stretching and toning 3 × 45 min exercise sessions per week over 12 months vs. usual care without exercise counseling) as described before [13,14].

For the purpose of the present study baseline results are reported on participants with complete sets of neuropsychological assessments (MoCA, CogState, TMT A and B, letter and category fluency tests), physical tests (LASA Physical Activity Questionnaire, LAPAQ, and Timed Up and Go, TUG) and lipophilic micronutrient plasma levels (retinol, six carotenoids and two tocopherols) as described below.

2.2. Neuropsychology

The MoCA, used as a broad measure of global cognitive function, is a one-page 30-point test administered in 10 min which consists of 13 tasks covering the following eight cognitive domains: visuospatial/executive functions, naming, verbal memory registration and learning, attention, abstraction, delayed verbal memory, and orientation. It has demonstrated high sensitivity and specificity as a cognitive screening instrument and has been validated to detect MCI [16]. Cognitive performance was assessed by a gamified computerized neuropsychological test battery measuring six cognitive domains. The test battery consisted of a computer-based CogState Battery including the International Shopping List Task (ISLT)—immediate and delayed recall, Detection Task, Identification Task, One Back Task (ONB), and One Card Learning Task (https://cogstate.com/) [18], verbal fluency [19,20] and Trail Making Test (TMT) [21].

Verbal memory was assessed by ISLT, *psychomotor function* by the Detection Task, *executive function* by TMT-B, Letter Fluency and Category Fluency. *Attention* was assessed by the Identification Task and TMT-A. *Working memory* was measured by One Back Task, and *Visual memory* by the One Card Learning Task. The ISLT is a 12-word, four-trial tests, where the total number of correct responses made in remembering the list on three consecutive trials at a single session and after a delay is recorded. The ISLT has been shown to have good sensitivity to verbal memory impairment [18]. The Detection Task measures psychomotor functioning and speed of processing. Participants must respond as quickly as possible, by pressing a keyboard button, when a playing card displayed on the computer screen shown face down flips over. Reaction time is measured with lower scores indicating better

performance. The Identification Task measures visual attention. Participants must decide whether a playing card presented on screen is red, by pressing the 'Yes' or 'No' button. Reaction time is measured and lower scores indicate better performance. The One Back Task assesses working memory. Participants are presented with a sequence of playing cards in the center of the screen and must decide if the card presented is the same as the one shown immediately before. The One Card Learning Task measures visual learning and memory. Participants are presented with a succession of playing card on screen, and must decide if the card currently displayed has been displayed previously. Accuracy of performance is measured, with higher scores indicating better performance. A number of studies have found that the CogState battery of tests are sensitive to detecting cognitive impairment in mild to moderate AD and amnestic MCI populations relative to healthy matched controls [18].

Verbal fluency was assessed by Letter Fluency [19] and Category Fluency [20]. For the Letter Fluency test participants were asked to generate in one minute as many words as possible beginning with a specific initial. This task was repeated three times with three different letters (e.g., L, B, S). For the category fluency test, participants must give as many examples of animals as possible within one minute. TMT [21] was completed as a paper-and-pencil-based task. The TMT consists of two sub-trials. TMT-A require individuals to sequentially connect 25 encircled numbers on a sheet of paper, while TMT-B require participants to draw a line, alternating between numbers and letters in ascending order.

2.3. Physical Activity Assessments

Physical activity and mobility were assessed through the Timed Up and Go (TUG) test [22] as well as through the self-reported LASA Physical Activity Questionnaire, which is a valid and reliable interview-administered questionnaire able to captures physical activity across six categories (walking outdoors, bicycling, gardening, light household activities, heavy household activities, and sport and exercise activities) over the preceding 14 days [23]. Mean daily activity scores, and mean time spent in sport and exercise activities were calculated by summing the reported activities in minutes and dividing those by the number of days.

2.4. Nutritional Analyses

For the nutrient analysis, the fruit and vegetable intake of each subject was calculated in grams. Subjects filled out a paper-based food frequency questionnaire ("Ernährungsfragebogen") used in the German Health Interview and Examination Survey for Adults (DEGS, "Studie zur Gesundheit Erwachsener in Deutschland") by the Robert Koch Institute. This questionnaire consists of 57 questions. Fifty-three questions are concerning the frequency of consumption of individual food items and the usual portion size when consumed; the remaining questions are to provide further detail on dietary patterns, such as the different types of fats/oils used and whether subjects do not eat certain foods. For each of the 53 questions concerning a food item, there are up to 3 sub-parts. Subjects are first asked how often they have consumed this item in the last 4 weeks (28 days). If they have consumed it at all, they are asked to indicate the usual portion size of the food item per intake. For some questions, they are asked a further qualitative question about the food item. Furthermore, for each question, the questionnaire provides a representative image of portion size for that food. The calculation of fruit and vegetable intake was as follows. The calculation for fruits took into account fresh fruit (e.g., apples, bananas) and preserved fruit (e.g., compote, canned fruit); the calculation for vegetables took into account fresh vegetables (e.g., lettuce, salads), cooked vegetables and pulses (e.g., beans, peas, lentils). After the exclusion process was complete, the amount of each food item consumed was calculated for the remaining subjects by multiplying the frequency of consumption with the portion size indicated in the questionnaire. Portion sizes were converted to gram amounts according to the reference values used in DEGS1 [24]. The gram amounts for the food items that made up the food groups "fruits" and "vegetables" respectively were then added together. For one subject, all three of the items that made

up the group "vegetables" were missing values, and so this subject's vegetable intake was considered as a missing value.

For the measurement of lipophilic antioxidant micronutrients, blood was collected in a heparinized tube and immediately centrifuged. Plasma was stored frozen at −80 °C until analysis, which was performed as described before [25]. Briefly, carotenoids including lutein, zeaxanthin, β-cryptoxanthin, lycopene, and α- and β-carotene were analyzed by HPLC with UV-vis detection at 450 nm according to Stahl et al. [26]. 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. Recovery from the column was 90% for each micronutrient. The calibration curves were linear from 0 to 1000 nmol/L for all carotenoids, with correlation coefficients 0·99. The intra- and inter-assay precision varied between 5 and 15%.

2.5. Statistics

For the statistical analysis, continuous variables are presented as mean ± standard deviation (SD), categorical variables as count and percentage. Correlations between plasma concentrations of micronutrients (lutein, zeaxanthin, β-cryptoxanthin, lycoepene, α-carotene, β-carotene, α-tocopherol, γ-tocopherol and retinol) and measures of cognitive (MoCA, CogState, TMT A and B, letter and category fluency tests) and physical performance (LASA Physical Activity Questionnaire, LAPAQ, and Timed Up and Go, TUG) were calculated using Pearson's correlation coefficient or partial correlation coefficient (r) controlled for fruit/vegetables intake. Statistical significance was defined as a two-tailed p value < 0.05. Data analysis was carried out with the SPSS/Win program version 23.0 (SPSS, Chicago, IL, USA).

3. Results

Of the 121 NeuroExercise study participants included at the GSU, 56 had the full dataset including neuropsychological assessment, physical fitness analysis, as well as plasma levels of micronutrients including retinol, six carotenoids, and two tocopherols. Demographic, neuropsychological, and physical characteristics of the study participants as well as their laboratory values are displayed in Table 1 and are in agreement with observations described in the literature [27,28].

Table 1. Demographic and clinical characteristics and laboratory values of the study participants.

Parameters	Values
Age (years)	73.1 ± 5.8
Gender [n (%) Female]	26 (46)
BMI	25.8 ± 3.4
Fruit and vegetable intake (g)	466 ± 371
LAPAQ (min)	229.8 ± 144.7
Steps/day	9895.7 ± 3714.7
TUG (s)	9.1 ± 1.5
MoCA (score 0/30)	23.2 ± 2.1
TMT A (s)	50.4 ± 20.6
TMT B (s)	145.4 ± 72.1
Letter Fluency (number of words/min)	11.6 ± 3.8
Category Fluency (number of words/min)	17.2 ± 4.6
DET (ms log10)	2.63 ± 0.09
IDN (ms log10)	2.80 ± 0.07
OCL (number of correct inputs)	64.8 ± 8.6
ONB (number of correct inputs)	89.6 ± 10.03
ISLT (number of recalled items)	20.6 ± 5.1
Lutein (μM)	0.46 ± 0.33
Zeaxanthin (μM)	0.08 ± 0.11
β-Cryptoxanthin (μM)	0.41 ± 0.47

Table 1. *Cont.*

Parameters	Values
Lycopene (μM)	0.51 ± 0.33
α-Carotene (μM)	0.10 ± 0.09
β-Carotene (μM)	0.74 ± 0.65
α-Tocopherol (μM)	28.9 ± 7.8
γ-Tocopherol (μM)	2.37 ± 0.84
Retinol (μM)	1.45 ± 0.42

The results of the analysis of the relationship between measures of cognitive (MoCA, TMT A, TMT B, Letter Fluency, Category Fluency and CogState) and physical (Activity Monitor, Number of Steps, LAPAQ, TUG) performance are displayed in Table 2.

Table 2. Significant correlations between measures of cognitive and physical performance.

	MoCA	TMT A	TMT B	LAPAQ	Steps	TUG	Letter Fluency	Category Fluency	CogState
MoCA		−0.6 <0.0001	−0.5 <0.0001		0.4 0.003	−0.3 0.005	0.35 0.001	0.5 <0.0001	ISLT: 0.6 <0.0001
TMT A			0.7 <0.0001		−0.3 0.03	0.3 0.02	−0.24 0.03	−0.46 <0.0001	IDNlog: 0.46 <0.0001 OCL: −0.3 0.009 ONB: −0.3 0.01 ISLT: −0.4 0.001
TMT B						0.4 <0.0001	−0.34 0.002	−0.45 <0.0001	DETlog: IDNlog: −0.42 <0.0001 OCL: −0.37 0.001 ONB: −0.38 0.001 ISLT: −0.38 0.001
LAPAQ									
Steps								0.34 0.009	ISLT: 0.26 <0.05
TUG							−0.34 0.004		ISLT: −0.3 0.009
Letter Fluency								0.48 <0.0001	ISLT: 0.3 0.009
Category Fluency					0.34 0.009				ISLT: 0.5 <0.0001

MoCA: Montreal Cognitive Assessment; TMT A and B: Trail Making Test A and B; TUG: Timed Up&Go.

When analyzing the associations between laboratory parameters and cognitive/physical measures, significant correlations independently of fruit and vegetable intake were found between plasma levels of β-cryptoxanthin and TUG ($p < 0.05$), γ-tocopherol and number of daily steps ($p < 0.01$), as well as four out of six measured carotenoids—lutein, zeaxanthin, β-cryptoxanthin, and β-carotene with ISLT ($p < 0.01$). (Table 3).

Table 3. Correlations between lipophilic micronutrients and physical/cognitive measures of the study participants. Adjusted for fruit and vegetable intake.

	r Value	*p* Value
β-Cryptoxanthin/TUG	−0.564	<0.05
γ-Tocopherol/Steps/day	0.525	<0.01
Lutein/ISLT	0.686	<0.01
Zeaxanthin/ISLT	0.723	<0.01
β-Cryptoxanthin/ISLT	0.603	<0.01
β-Carotene/ISLT	0.660	<0.01

Finally, we were able to identify two groups of individuals based upon micronutrient levels. The first group (7 subjects) was called "supermicro" as persons displayed all micronutrient levels above the median value (the Boolean AND operation was used in the selection algorithm). These were compared to the group of the remaining 49 participants. This comparison underlined the supermicro group as indeed better both physically (Timed Up&Go test, 8.0 ± 0.9 s vs. 9.2 ± 1.4 s, $p = 0.002$) and cognitively (One card learning subtest of the CogState, 58.6 ± 8.3 vs. 65.7 ± 8.4, $p = 0.04$) performing than the rest of the participants.

4. Discussion

The main result of the present study is that plasma levels of several lipophilic antioxidant micronutrients are significantly associated, independently of fruit and vegetable intake, with validated, accurate measures of both cognitive and physical performance in persons with MCI. To our knowledge, no studies have so far explored a broad spectrum of the most robust biomarkers of nutrition and antioxidant defense in clinically highly characterized patients comprehensively assessed as far as both cognitive and physical performance are concerned. In particular, the use of a large battery of neuropsychological tests including a validated, accurate gamified computerized testing with high clinimetric properties (CogState) allows a detailed description of the association between selected micronutrients and specific cognitive abilities. This represents a further step in the field of nutritional cognitive neuroscience [29]. Carotenoids are robust biomarkers of dietary exposure which have been previously shown to be associated with global measures of cognition [27,30] and lipid profile in patients with cognitive impairment with and without dementia [28,30–32]. In addition, selected tocopherols and carotenoids have been shown to be directly associated with fruit and vegetable intake [28,33] as well as positively associated with cognitive performance and inversely associated with markers of oxidative stress in healthy subjects independent of age, gender, and fruit/vegetable intake, suggesting their protective role even in the absence of disease [27,28]. In the present study, plasma concentrations of several carotenoids were strongly correlated with the ISL task of the CogState battery, a valid gamified computerized testing method of which the ISL sensitively and reliably measures verbal learning and memory [18]. Interestingly, a significant association was previously found in persons with subjective cognitive impairment (SCI) between the ISLT and the endothelial peripheral arterial tonometry index (EndoPAT Index), a measure of endothelial function [34], considered an important mediator of cognitive impairment [8]. In addition, it should be considered that the present observations are in strong agreement with previous reports of a relationship between higher plasma concentrations of lipophilic micronutrients and specific high cortical functions, in particular immediate memory and measures of global cognition [28,30–34]. The association of plasma concentrations of circulating protective micronutrients—no matter whether as markers of nutritional exposure or pure indicators of defense against redox imbalance and oxidative stress (Table 3)—with both physical and cognitive performance reflect the tight relationship between these two families of functions, and has recently been the object of great attention and also confirmed in the present investigation (Table 2).

Interestingly enough, among 331 candidate (bio)markers investigated in the MARK-Age study, lower levels of β-cryptoxanthin and zeaxanthin were found, among 2220 randomly recruited

age-stratified persons, in those who were physically, cognitively, or psychologically frail [35]. In this study, levels of β-cryptoxanthin and zeaxanthin were inversely associated with risk of being cognitively frail after adjusting for confounders. In our study, plasma levels of β-cryptoxanthin were also correlated with the TUG test, a marker of balance and increased fall risk and of physical frailty. Carotenoids may indicate the involvement of oxidative stress and inflammation in frailty, both physical and cognitive.

It is important to briefly point on the biochemistry of carotenoids to better understand their special role in nutritional cognitive neuroscience. As natural pigments present in plants, animals, and microorganisms, carotenoids reduce reactive byproducts such as reactive oxygen species (ROS) thereby acting as antioxidants. ROS, like other free radicals, are known to be potent mediators of neurodegeneration [8]. Carotenoids' polarity - xanthophylls such as astaxanthin, β-cryptoxanthin, lutein, and zeaxanthin are polar while carotenes such as α-carotene, β-carotene, and lycopene are nonpolar- determines their differential distribution in the human body, with xanthophylls accounting for 66–77% of the total carotenoids in the frontal and occipital lobes of the human brain [30]. In addition, lutein and zeaxanthin are the only two carotenoids that cross the blood–retina barrier to form macular pigment in the eye [36] and lutein is the dominant carotenoid in human brain tissue [37–39]. These biochemical characteristics strongly indicate that these micronutrients are determinant for nervous tissue physiology and functioning. Furthermore, lutein is the major carotenoid in brain tissue despite not being the major carotenoid in matched serum (an indicator of dietary intake), which implies a preferential uptake into brain tissue [39]. Lutein and zeaxanthin in macula were found to be significantly correlated with their levels in matched brain tissue in primates [40], suggesting that macular pigment can be used as a biomarker in brain tissue. This is of interest, given that a significant correlation was found between macular pigment density and global cognitive function in healthy older adults [41,42]. In brain tissue of decedents from a population-based study, lutein was found to be consistently associated with a wide range of cognitive measures [43] which, similar to our study, included executive functions, language, learning, and memory. These functions were in turn found to be specifically associated to carotenoid contents in specific brain regions.

The main limitation of our study is the low sample size. However, the observed values of micronutrient status, cognitive and physical ability are in agreement with those present in the literature. In addition, the accurate inclusion and exclusion criteria as well as the very comprehensive neuropsychological battery and the use of the most robust biomarkers of dietary exposure measured through high performance analytics guarantee the interpretability of the results. Another issue might be that, although the evidence for a role of carotenoids in cognitive function is accumulating, the studies discussed thus far, including the present one, are correlative and do not demonstrate cause and effect. However, in a double-blinded, placebo-controlled trial of women who received lutein supplementation (12 mg/d), docosahexaenoic acid supplementation (800 mg/d), or a combination of the two for 4 months, verbal fluency scores improved significantly in all three treatment groups. Memory scores and rates of learning improved significantly in the combined treatment group, who also displayed a trend toward more efficient learning [43]. Taken together, these observations suggest that at least lutein could influence cognitive function.

In conclusion, plasma levels of carotenoids were shown to be significantly associated with indices of both physical and cognitive frailty in the present study. In light of the increasing attention towards the nutritional cognitive neuroscience of carotenoids [44,45] as well as the vascular component of nutritional cognitive neuroscience [6–8,10,11,27–34,46], the use of computerized measures of cognitive performance might be further implemented in future studies investigating the effects of lifestyle interventions against cognitive and physical impairment.

Author Contributions: P.G. and M.C.P. conceived the paper; G.N., R.K.P., B.W., H.W., T.S., S.S., L.S., and M.C.P. conceived the methodology of analysis of data; P.G., R.K.P., L.S., S.S., and M.C.P. contributed to the analysis including statistics; P.G., T.S., and M.C.P. conducted the assessments; T.S., S.S., R.K.P., and B.W. created and managed the database; J.F., R.K.P., T.S., and M.C.P. wrote the manuscript; G.N., W.S., and B.W. contributed to the planning and collection of data and operated critical reviewing of the manuscript; S.S. and M.C.P. fully supervised the analyses and writing.

Funding: The NeuroExercise studies are supported by The EU Joint Programme – Neurodegenerative Disease Research (JPND). German grant number BMBF 01ED1510A.

Conflicts of Interest: The authors declare no conflict of interest.

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5. Discussion

In the present study, we investigated the association between cognitive and physical performance and the levels of various micronutrients in individuals with MCI. The present findings underscore a notable association between circulating levels of a broad range of lipidsoluble antioxidant micronutrients and both cognitive and physical performance among individuals with MCI.

Early stages of cognitive impairment such as subjective cognitive impairment (SCI) [234], age-related cognitive impairment [235] and MCI [236] are associated with an elevated risk of progression to dementia compared to the general population. Reported annual conversion rates range between 10% and 15% [237, 238]. Cognitive impairment is typically characterised by deficits in domains such as memory, executive function, language, and attention that exceed age- and education-adjusted expectations, and may compromise an individual's capacity to perform everyday activities independently [239]. Furthermore, cognitive impairment with or without dementia is a multifactorial syndrome rather than a single one cause–one mechanism disease. For this reason, when observing the patterns of micronutrient profiles, it is essential to acknowledge that different variables such as metabolism, distribution and bioavailability, as well as dietary supply, depend on individual host factors, including age, gender [87], lifestyle [249], genetic makeup and diseases [206].

Due to the multifaceted pathophysiology of cognitive impairment, an effective treatment strategy for most individuals with cognitive impairment cannot be achieved by a single intervention but rather requires a comprehensive, multidimensional approach. Medical care for dementia patients is based on four pillars affecting the disease's progression and impact: early diagnosis, comprehensive evaluation of symptoms and impairment assessment, precise staging and continuous monitoring of disease progression, and the individualised adjustment of therapeutic strategies [241].

The diagnosis of dementia is often delayed because the neurodegenerative changes associated with dementia can begin up to 30 years before the onset of clinical symptoms, which are often inaccurate due to the broad and unspecific character [21]. AD, traditionally diagnosed through clinical evaluations and supported by neuroimaging and cerebrospinal fluid (CSF) analyses, has seen a paradigm shift with the introduction of biomarker-based diagnostics. Recent findings illuminate a critical transition towards a more nuanced understanding of AD, focusing on the biological underpinnings of the disease. The preference for CSF biomarkers by clinicians underscores their perceived diagnostic value, mirroring the current scientific consensus on their utility in reflecting the pathological hallmarks of AD. However, the relatively limited use of amyloid-PET and tau-PET, along with the differing

opinions on the pathogenic roles of amyloid and tau, highlight the complexities and ongoing debates within the field regarding AD pathophysiology and diagnosis [250].

Jessen et al. suggest a changing clinical landscape, where traditional and emerging biomarkers coexist, reflecting both the advances in our understanding of AD and the practical challenges of integrating new diagnostic tools into routine clinical practice. As AD research progresses, the ongoing dialogue among clinicians, researchers, and policymakers to harmonise diagnostic practices, optimise patient care, and pave the way for the introduction of disease-modifying therapies is of great importance [250].

In the context of pharmacological interventions [254], research has shown that while approaches to reduce amyloid plaques and tau proteins are promising [19], further validation is needed to confirm their efficacy and safety across broader patient populations. The ongoing debate around Aducanumab [257] and the exploration of alternative therapeutic targets emphasise the complexity of disease mechanisms and the necessity for diversified research approaches. Furthermore, several pharmacological medications have been proposed in recent years to prevent and treat AD, without a definitive disease-modifying treatment to this day. Due to the current lack of effective treatments for age-related cognitive decline, the focus has shifted towards methods of early detection and prevention of cognitive frailty with lifestyle approaches representing a promising avenue for further development [17,241].

The exploration of risk factors for cognitive impairment extends beyond lifestyle-associated risks (e.g. hypertension, obesity, hearing loss, smoking, diabetes mellitus) to include iatrogenic and somatic factors. These risk factors contribute not only to the complexity of cognitive disorders but also to the opportunities for intervention and prevention [255]. The lifestyle-associated risk factors, particularly the "population attributable fraction" for each, highlight the significant potential for preventing AD by modifying risk factors. This perspective is further substantiated by the latest WHO guidelines, which advocate a structured framework for reducing dementia risk. Particular emphasis is placed on the holistic consideration of both lifestyle-related factors and chronic health conditions [255]. The difficulty lies in translating this knowledge into effective public health strategies. The diversity of risk factors and the individual variability in risk profiles necessitate personalised intervention strategies, a concept that presents its own set of challenges in terms of development, implementation, and scalability [255].

Cognitive decline is multifaceted in nature and brings with it the need for a comprehensive, multidisciplinary approach to prevention and management. Addressing cognitive decline effectively requires a nuanced understanding of the interplay between neurology, systemic health, lifestyle factors, and individual risk profiles. While the challenges are significant, innovative approaches to public health policy and personalised health management will be

crucial in translating this foundational knowledge into effective strategies for reducing the burden of cognitive decline [255].

Given that the present study is a sub-study of the NeuroExercise multi-centred randomised controlled trial, similarities in the findings, yet certain differences can be identified. The comprehensive initial analysis of the Neuroexercise study did not reveal any statistically significant impact of the intervention on cognitive performance in individuals with MCI. However, after a 12-month exercise intervention, a consistent impact on physical fitness could be shown, which might play a crucial role in the progression of the disease and warrants further long-term follow-up.

We found that micronutrients were primarily associated with cognitive measures before the physical intervention. In contrast, the main associations in the post-intervention statistics were observed between micronutrient status and physical fitness variables, which is in agreement with those present in the literature [204, 221, 224, 273, 226, 228]. Based on this premise, it can be inferred that these relationships, particularly those related to micronutrient status, could potentially provide insights into physical fitness after a 12-month exercise intervention. Previous studies have also shown associations between carotenoids and cognitive measures, as well as a potential role for these compounds in vascular function and cognitive impairment. Thus, the use of micronutrients as markers for lifestyle strategies becomes a potential avenue, given the observed influence of physical exercise on the antioxidant defence mechanism of the body.

In contrast to some previous research, our study emphasises the independent associations of micronutrient levels with cognitive and physical performance measures, regardless of fruit and vegetable intake, which is commonly correlated with higher micronutrient levels. This suggests a direct relationship between these specific micronutrients and cognitive function, beyond what might be contributed by a generally healthy diet rich in fruits and vegetables.

The findings of our study demonstrated robust associations between circulating concentrations of carotenoids and performance outcomes across both cognitive and physical domains in individuals diagnosed with MCI. It supports and extends findings from prior research indicating a beneficial role for lipophilic micronutrients in maintaining cognitive and physical function in older adults, particularly those with MCI. These findings align with the burgeoning field of nutritional cognitive neuroscience and underscore the potential role of micronutrients in brain health. The study's innovative approach, including the use of a comprehensive neuropsychological battery and robust biomarkers of dietary exposure, contributes valuable insights into the interplay between nutrition and cognitive function.

Parallel to nutrition, physical fitness emerges as a critical factor in maintaining and enhancing cognitive health. The study elaborates on how sedentary lifestyles are linked with increased risks of dementia, and how regular physical activity can mitigate these risks. Notably, aerobic exercises have been shown to induce neurogenesis, improve blood flow, and increase volume in the hippocampus, a brain area pivotal for memory and learning. This connection between physical fitness and cognitive health underlines the importance of incorporating regular physical activity into daily routines as a means to support cognitive resilience [255].

The interplay between nutrition and physical fitness in influencing cognitive health points to the need for comprehensive lifestyle interventions. These interventions should address not only dietary habits and physical activity but also consider other lifestyle factors like social participation and cognitive training. The potential of such multidomain lifestyle interventions in maintaining cognitive function and delaying the progression of dementia is immense. Implementing these interventions requires concerted efforts from healthcare providers, policymakers, and individuals to foster environments conducive to healthy living [255].

Cognitive integrity is not only pivotal for quality of life and well-being but is intrinsically linked to significant life outcomes, including academic success, job performance, and even health morbidity and mortality. The BrainProtect® programme, by addressing cognitive performance through a holistic lens, taps into this urgent need for strategies that not only forestall dementia but also enhance the broader spectrum of cognitive health as a critical component of active ageing [256].

The BrainProtect® programme stands out by integrating cognitive exercises with physical and nutritional counselling, grounded in the understanding that cognitive health is influenced by a complex interplay of factors. This multidomain approach aligns with emerging evidence suggesting that interventions targeting multiple aspects of lifestyle can synergistically improve cognitive functions. As the population ages, the demand for effective, evidencebased interventions to preserve and enhance cognitive health will only grow. Programmes like BrainProtect® offer a blueprint for such interventions, blending cognitive, physical, and nutritional strategies to support cognitive integrity and active ageing. By fostering cognitive integrity through integrated cognitive training, physical exercise, and nutritional counselling, such programs can play a crucial role in public health strategies aimed at combating cognitive decline [256].

Another study by Zeyen et al. outlines the operational framework of the Cologne Alzheimer Prevention Centre (KAP), showcasing how it exemplifies the implementation of brain health services in Germany. Through a multifaceted programme, the center aims to identify individual dementia risk profiles, communicate these risks effectively to participants, and develop

personalised prevention strategies. The programme responds to the WHO´s call for dementia prevention and care strategies, reflecting a paradigm shift towards early identification and intervention [14].

A notable component of the KAP's approach is the systematic assessment of a wide range of modifiable risk factors, including lifestyle choices (e.g., diet, physical activity, sleep quality) and medical conditions (e.g. hypertension, diabetes), through a comprehensive questionnaire and physical examination. The findings of the study indicate a high prevalence of modifiable risk factors, including non-adherence to a Mediterranean dietary pattern, obesity, poor sleep quality, and elevated stress levels. These observations underscore the importance of implementing targeted interventions to mitigate such risks and promote cognitive resilience [15].

This research underscores the importance of creating specialised centers like the KAP to bridge the gap in dementia prevention services, especially for individuals without overt cognitive impairments seeking information on reducing their dementia risk. Such centers play a crucial role in raising public awareness, offering evidence-based prevention advice, and conducting research to refine and validate personalised intervention strategies. The study calls for further research to evaluate the efficacy of personalised prevention programmes and highlights the need for sustainable funding mechanisms to integrate these services into regular healthcare provision. Ultimately, this approach represents a promising avenue for reducing the burden of dementia through early risk identification and tailored preventive interventions, paving the way for a more proactive and precision-based model of care [15].

Within the existing body of knowledge, no research has yet comprehensively investigated a wide range of robust nutritional and antioxidant defence biomarkers in clinically wellcharacterised patients, in relation to both cognitive and physical performance. In order to investigate the association between specific cognitive abilities and selected micronutrients, a large battery of neuropsychological tests including a validated and accurate gamified computerised testing with high clinimetric properties (CogState) was used. However, a limitation mentioned is the reliance on these specific tools without discussing their validation against other standard cognitive assessments. While the CogState Battery is noted for its sensitivity in detecting cognitive impairment, the validation of these tools in the context of assessing the impact of nutritional interventions on cognitive performance is crucial for interpreting the study's findings accurately.

The main limitation of our study is the small sample size, which might affect the generalisability of the findings and their statistical power. An expanded cohort would likely increase the reliability of the observed associations between plasma levels of specific micronutrients and

improvements in cognitive and physical performance. The ramifications of a limited participant pool highlight the need for caution in extrapolating these conclusions to a broader population. Moreover, the study's correlative nature restricts the ability to infer causality from the identified associations. Although significant correlations between certain micronutrient concentrations and cognitive or physical enhancements were documented, it remains uncertain whether augmenting the intake of these micronutrients would directly lead to improvements in cognitive functions or physical fitness. This limitation accentuates the necessity of conducting interventional studies designed to establish direct causal relationships and to dissect the mechanisms underpinning the observed correlations.

Another considerable limitation of our study to consider is that our findings are correlational and do not demonstrate a cause-and-effect relationship. Despite emphasising the independence of associations from fruit and vegetable intake, the broader context of participants' dietary patterns and lifestyle factors remains a confounding variable. The study provides evidence of an association between carotenoids and cognitive function, but it does not conclusively demonstrate that carotenoids directly cause improvements in cognitive function. The overall diet, physical activity, social engagement, and other lifestyle factors could significantly impact cognitive function and physical performance.

Addressing these limitations in future research is critical for advancing our understanding of the role of nutrition in cognitive health. This limitation is important as it suggests the need for further research to establish a direct causal relationship, to uncover the complex interplay between diet, lifestyle, and brain health. Larger, randomised controlled trials with validated cognitive assessment tools are needed to confirm the findings and explore the mechanisms underlying the observed associations. Moreover, longitudinal studies could provide insight into how changes in micronutrient levels over time relate to cognitive and physical performance outcomes. While the study offers promising insights into the potential impact of lipophilic micronutrients on cognitive and physical fitness in individuals with MCI, its limitations underscore the need for cautious interpretation of the results and further research to validate and expand upon these findings.

However, the measured values of micronutrient plasma levels, cognitive and physical performance align with those reported in the existing body of knowledge. There are also strengths to our study, such as: in order to ensure the interpretability of the results, a significantly comprehensive neuropsychological test battery, a precise selection of inclusion and exclusion criteria and the most robust biomarkers of dietary exposure analysed through cutting-edge analytical techniques were used. To create a more reliable and valid psychometric concept, an overall score for cognitive function, defined as the primary outcome, was derived by combining various cognitive tests and different subdomains of cognitive function.

Despite the correlational nature of the study and the limitation of the small sample size, the results are consistent with existing literature and suggest a protective role for carotenoids, independent of fruit and vegetable intake. The reciprocal relationship between diet, physical activity, and cognitive health posits that micronutrient levels can influence physical fitness, which in turn could impact cognitive function. This assumption aligns with the broader discourse on nutritional cognitive neuroscience, suggesting that lifestyle interventions incorporating physical exercise and dietary adjustments could mitigate the risks of cognitive and physical impairments in ageing populations. This reinforces the importance of considering dietary interventions as part of strategies to mitigate cognitive and physical decline. Future research could further elucidate the direct impacts of micronutrients on cognitive performance and the overarching benefits of a holistic lifestyle approach in combating cognitive decline. The integration of computerised cognitive assessment tools has been recognised as a promising avenue for future investigation, particularly within the framework of lifestyle-based interventions aimed at counteracting cognitive impairment.

Nevertheless, our findings have important implications for the prevention and management of cognitive decline, supporting the hypothesis that targeted nutritional strategies may enhance cognitive resilience. This work adds a significant piece to the puzzle of how diet influences brain health and encourages future research.

6. Conclusion

The future perspective on dementia incorporates a multifaceted approach that acknowledges the complexity of the condition. This integrates factors ranging from diagnosis and treatment to the social environment, each playing a crucial role in managing and potentially mitigating the progression of dementia-related impairments.

While the ageing process, particularly the ageing brain, is multifactorial and heterogeneous [233], multidimensional approaches will lead to a better understanding of its complexity. The rising prevalence of dementia-related impairments, driven by demographic changes, represents an increasing burden on global health systems, thus reinforcing investigation in the field of cognitive decline. The importance of early diagnosis, particularly of AD, through biomarkers and imaging techniques, is undeniable. Advances in blood-based biomarkers offer new possibilities for early diagnostics, potentially marking a turning point in the accessibility and efficiency of diagnostic methods [252]. These advancements are crucial for the early identification of at-risk individuals and the initiation of preventive and therapeutic measures.

Non-pharmacological therapy approaches, including cognitive interventions and physical activity, have proven effective in delaying disease progression and enhancing the quality of life for affected individuals [2, 253]. As previous studies have already shown, Veronese et. al also demonstrated that physical activity and exercise represent vital components in the multifaceted approach to dementia, including its prevention and management. The implications of this research are substantial, affirming that even modest levels of physical engagement could potentially modify the trajectory of cognitive decline in individuals across a spectrum of cognitive abilities, from robust ageing to those experiencing the subtle onset of MCI, and further into the various stages of dementia [259].

Furthermore, the study underscores that, while the pathophysiological underpinnings are complex, the synergistic effects of physical activity and exercise on cognitive function appear to be mediated through a multitude of mechanisms, including improved vascular health, upregulation of neurotrophic factors, reduction in inflammatory markers, and perhaps most compellingly, the promotion of neuroplasticity. The latter is particularly important as it offers a biological basis for the observed cognitive benefits, with exercise-induced neurogenesis in critical areas such as the hippocampus, which is a region heavily implicated in memory and learning [259].

However, despite these promising findings, there remain significant barriers to the broad application of exercise and physical activity as therapeutic modalities in dementia care. These range from individual patient factors, such as the degree of cognitive impairment and physical comorbidities, to systemic issues, like the accessibility of suitable programs and the training of caregivers and healthcare providers to implement and support sustained physical activity regimens [259].

From a research perspective, while the existing body of evidence provides a compelling narrative supporting the role of physical exercise in cognitive health, there is a critical need for future investigations to delineate the optimal types, intensities, and durations of exercise that confer the greatest benefit. Moreover, given the heterogeneity of dementia, understanding the differential impacts of physical activity across various dementia subtypes, stages, and individual patient profiles will be crucial in refining recommendations and maximising therapeutic efficacy.

In envisioning the future of dementia care, it becomes clear that a paradigm shift is warranted, one that moves beyond the traditional reliance on pharmacological interventions alone to an integrative model that holistically incorporates physical activity and exercise as foundational elements. The trajectory of this shift will be informed by forthcoming highquality, randomised

controlled trials that offer granular insights into the nuanced relationships between exercise and cognitive outcomes.

Researchers, clinicians, patients, and policymakers are asked to embrace a proactive stance on exercise, recognising its vast potential not only as a means to enrich the quality of life among the elderly but as a strategic tool to potentially stave off the cognitive decline associated with the dementia spectrum [259].

Another study by Polidori [260] examines the interplay between intrinsic ageing processes and external factors such as lifestyle, socioeconomic status, and psychological well-being. It suggests that the pathogenesis of dementia, including AD, may be as much about managing the body's repair mechanisms and resilience as it is about treating the symptoms of the disease [260]. Dementia, as an exemplar of an age-related condition, is not merely the outcome of pathological neurodegeneration but is intricately linked with systemic physiological changes that accompany ageing. Therefore, managing dementia requires a confluence of strategies that target both the biological underpinnings and the clinical manifestations [260].

The rise of ageing hallmarks and biomarkers is a testament to the scientific community's efforts to quantify and qualify the ageing process. Biomarkers offer a measurable reflection of biological age versus chronological age, capturing the essence of the individual's health span. The future of dementia care must leverage these biological markers, incorporating them into comprehensive assessments that can guide interventions aimed at modulating the rate of ageing. Such strategies might include dietary adjustments to address micronutrient deficiencies, as implicated by the correlation between specific carotenoids and cognitive performance [260].

Furthermore, the exploration of redox biology in ageing presents an intriguing facet of dementia research. The oxidative stress theory, which has seen conflicting results in the past, might find its place in a more nuanced understanding of the redox balance within the body. Rather than seeking a panacea in antioxidants, future research should focus on the balance of oxidative and reductive processes as they naturally occur within the body's milieu.

To distill this understanding into practical applications, interdisciplinary collaborations are paramount. Gerontologists, biogerontologists, neuroscientists, and clinicians must unify their perspectives to develop interventions that address the multidimensional nature of ageing and dementia.

As we step forward, there's a hopeful vista that sees geroprotective strategies emerging from the alignment of ageing science and clinical practice. By decoding the complex network of

factors that contribute to dementia, we aim to forge ahead into an era where ageing is not synonymous with cognitive decline, but rather a phase of life where quality and vitality are sustained through science-backed, personalised interventions [260].

Recent studies open the door to a future where the convergence of ageing research and dementia care fosters a new paradigm in the management of ageing populations. These studies also indicate a shift towards multidomain strategies that embrace the complexity of human ageing and employ the full spectrum of ageing biomarkers, hallmarks, and clocks, offering a blueprint for a future where ageing is navigated with dignity and cognitive vitality is preserved [260].

Promoting public and political awareness of dementia as one of the greatest health challenges of our time is crucial to securing the necessary resources for research and care. Close collaboration among scientists, clinicians, patient organisations, and policymakers will be essential to developing effective prevention strategies, improve care for affected individuals, and ultimately accelerate the development of curative therapies.

The identification and assessment of modifiable risk factors for dementia highlight a shift towards a more preventative approach in managing dementia, acknowledging that interventions in lifestyle and health behaviours have the potential to significantly reduce dementia incidence. The integration of genetic risk factors into dementia risk profiling is another critical aspect. Ranson et al. show how common and rare genetic variants, particularly those associated with AD, influence dementia risk. This genetic dimension adds a layer of complexity to risk profiling, suggesting that personalised prevention strategies could be more effective, especially in individuals with a higher genetic predisposition to dementia [261].

In terms of practical application, the study outlines a protocol for assessing risk factors within Brain Health Services (BHSs), including the use of multidomain risk prediction models and the assessment of additional fluid and imaging biomarkers. This comprehensive approach not only facilitates the identification of individuals at risk but also paves the way for tailored interventions that could delay or prevent the onset of dementia symptoms [261].

The discussion of existing dementia risk prediction models, such as the Cardiovascular Risk Factors, Ageing and Incidence of Dementia (CAIDE) score, and the Australian National University Alzheimer’s Disease Risk Index (ANU-ADRI), reflects ongoing efforts to develop tools that can accurately predict dementia risk. These models, while not without limitations, represent important steps towards understanding and mitigating the multifaceted nature of dementia risk [261].

The current body of evidence does not provide efficient support for any specific or general recommendations regarding drug- or compound-related prevention of cognitive decline or dementia. It is imperative to acknowledge that conducting prevention trials on cognitive decline in ageing and dementia requires large cohorts of participants and extensive follow-up periods, posing significant challenges in terms of both execution and funding. Furthermore, ethical considerations regarding the administration of medications, particularly in elderly populations, add complexity to the study design.

In addition, the development of new therapeutics needs to be guided by deeper insights into the molecular and cellular mechanisms of disease onset and progression. A stronger integration of technological innovations, such as artificial intelligence and machine learning, into research and clinical practice could help optimise diagnostic and treatment strategies. Given these challenges and limitations, it is not surprising that clear recommendations for pharmacological prevention strategies have yet to emerge. Instead, while further research is needed to fully understand and maximise the potential of non-pharmacological approaches, current data indicate that they represent a promising strategy for dementia prevention. Such approaches include lifestyle interventions such as physical activity, cognitive stimulation, social interaction, and healthy nutrition [258]. These methods have the potential to reduce the risk of developing dementia or slow its progression and are often associated with fewer risks and side effects than pharmacological treatments. This underscores the importance of a holistic approach to promoting cognitive health in ageing, which encompasses not only pharmacological interventions but also the promotion of healthy lifestyles and social engagement.

The perspective of this study is grounded in the field of nutritional cognitive neuroscience, with a particular focus on implementing micronutrient interventions for the prevention or delay of cognitive decline. Our study is positioned at the crossroad of nutrition, gerontology, and brain health, providing a new perspective for exploring the relationship between micronutrient components and cognitive function.

A comprehensive intervention that incorporates both nutritional and physical components could yield significant cognitive benefits for individuals at risk of dementia. The ultimate objective might be multifactorial lifestyle changes to optimise the prevention of cognitive decline in a personalised medicine approach.

From this perspective, the study not only seeks to shed light on the associations between micronutrients and cognitive health, but also to encourages a renewed focus on modifiable dietary factors that could contribute to cognitive robustness in ageing populations. The findings present a compelling argument for the inclusion of nutritional strategies in public health policies aimed at addressing the growing challenge of cognitive impairment in older adults. The study

highlights the need for larger-scale, longitudinal research to validate and expand upon the findings and for randomised controlled trials to explore causality and the efficacy of specific nutritional interventions.

The implications of such research are profound, with the potential to shift the current treatment paradigms for cognitive decline and towards prevention and early intervention. It suggests that future research should not only continue to explore the role of individual micronutrients but also the synergistic effects of whole dietary patterns, the impact of nutrient bioavailability and the influence of individual differences in metabolism and genetics on nutrient efficacy. The potential of these insights to inform clinical practices, shape public health policies and drive future projects marks an important step forward in our quest to enhance cognitive health and quality of life among older adults. Enhancing our understanding of the multifactorial nature of cognitive decline—particularly with regard to nutritional status and physical activity—offers a promising foundation for more targeted approaches to prevention and care. Although the challenge of addressing cognitive impairment and dementia remains complex, it is accompanied by considerable potential for progress through sustained scientific inquiry, interdisciplinary collaboration and evidencebased public health strategies.

7. References

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8. Preliminary publication of results

- Original Paper: Associations of Lipophilic Micronutrients with Physical and Cognitive Fitness in Persons with Mild Cognitive Impairment by Gerger P, Pai RK, Stuckenschneider T, Falkenreck J, Weigert H, Stahl W, Weber B, Nelles G, Spazzafumo L, Schneider S, Polidori MC (04/2019)