Micronutrients, frailty and Cognitive Impairment:
Design and preliminary results from the CogLife 2.0 study

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ABSTRACT

Among crucial preventive strategies against dementia, nutrition is considered a powerful one and the recently established “nutritional cognitive neuroscience of aging” is a highly active research field. The present study was designed to deeply characterize older adults across the continuum from cognitive integrity to mild cognitive impairment (MCI) and better elucidate the prognostic role of lipophilic micronutrients within their lipidomic signature. To do so, 123 participants older than 65 years across the continuum from cognitive integrity to MCI were included [49 with subjective cognitive impairment (SCI), 29 women, 72.5±5.4y, 26 MCI, 9 women, 74.5±5.8y and 50 without cognitive impairment (no CI, NCI), 21 women, 70.8±4.3y]. All participants underwent neuropsychological and nutritional examination as well as comprehensive geriatric assessment (CGA) with calculation of the Multidimensional Prognostic Index (MPI) as a proxy of frailty and biological age and blood withdrawal for the analyses of lipophilic micronutrients (carotenoids, α-tocopherol and retinol), metabolomics and oxylipidomics. One year after the evaluation, same tests are ongoing, including blood sampling. After adjustment for age, sex, daily fruit and vegetable intake, we found a significant positive correlation between lutein and the number of correct words in category fluency (p=0.026). This result supports the importance of carotenoids as robust biomarkers of cognitive performance independent of the nutritional status and frailty of the participants, as the entire present study collective was robust (MPI 0-0.33). The complete analyses of the metabolome and the oxylipidome will hopefully shed light on the metabolic and prognostic signature of cognitive decline in the rapidly growing population at risk of frailty.

KEYWORDS: Micronutrients, Alzheimer´s Dementia, dementia, Mild Cognitive Impairment, Subjective Cognitive Impairment, Frailty

BACKGROUND

As life expectancy increases worldwide, the frequency of diagnoses of non-communicable diseases, such as dementia, diabetes type 2 and chronic kidney failure, is also on the rise [1]. Dementia is particularly worrying -while there are various new treatment approaches for age-related chronic kidney disease or type 2 diabetes mellitus (e.g. SGLT-2 inhibitors [2, 3] or GLP-1 analogues [4]), there is still no curative approach for dementia. The long-awaited anti-amyloid monoclonal antibodies aducanumab [5] and lecanemab [6], which have been approved by the FDA in the USA for the treatment of Alzheimer's Disease (AD), are able to slow down the progression of the disease, but not to cure it. Hence, the focus of anti-dementia strategies is still predominantly prevention [7, 8], and clinical entities such as subjective cognitive impairment (SCI) and mild cognitive impairment (MCI) are under the spotlight with this purpose [9-11]. Among preventive strategies, nutrition is considered a powerful one and the recently established field of "nutritional cognitive neuroscience of aging" is highly active [12, 13]. However, the role of nutrients in cognitive impairment is difficult to address, due to biomolecular complexity, typically difficult deep phenotyping of study participants, and lack of detailed longitudinal information, especially in advanced age [14-16]. In addition to the evidence of a role of micronutrients, especially carotenoids, in cognitive frailty [12, 17, 18] – involving oxidative stress control [8, 10, 19] – and the fact that they can be influenced by diet and exercise [13, 14]-, the metabolome, especially the lipidome, is becoming more and more focus of preventive dementia research [11, 20-24]. However, complexity of (brain) aging often hinders clear interpretability of the role of micronutrients in health and disease, as micronutrient status is influenced by a wealth of components and age-related cognitive frailty is multifactorial [25]. The aim of the CogLife 2.0 study was therefore to deeply phenotype older adults in the continuum from cognitive integrity to MCI to identify biomolecular, nutritional and functional factors associated with longitudinal changes in cognitive performance.

PATIENTS AND METHODS

Study design

CogLife 2.0 is a longitudinal observational study of 150 volunteers recruited by advertisement, of which 50 healthy (no cognitive impairment, NCI), 50 with SCI and 50 with MCI. The study was conducted in accordance with the Declaration of Helsinki (1975) and approved by the Research Ethics Committee of the University of Cologne (EC:22-1379) in January 2023. The trial was registered in the German Clinical Trials Register DRKS (DRKS00030000). Contacts were made via a register at Cologne University Hospital, in which people who had indicated an interest in participating in clinical trials could sign in. In addition, information was distributed to several neurological practices in the Cologne area and via a senior citizens' network in Cologne. Participants who had previously taken part in other studies regarding neurocognition conducted by the same research working group were informed about the “CogLife 2.0” study, provided they had agreed to be contacted again.

Participants

Recruitment of participants began on February 13th, 2023. Participants were eligible if they were aged 65 years and older and were interested in learning more about their cognitive health. Further inclusion criteria were absence of life-threatening, psychiatric or neurological disorders other than neurocognitive impairment, a Montreal Cognitive Assessment (MoCA) - score between 18 and 30, no relevant comorbidities (measured by a Cumulative Illness Rating Scale - Geriatric (CIRS-G) - score of 2 or less), absence of over- or underweight (Body Mass Index (BMI) ≥18 and ≤30 kg/m^2), absence of vitamin/antioxidant supplementation (except cholecalciferol, Vitamin D supplements) and not following a vegetarian or vegan diet, adequate visual, auditory and linguistic acuity to complete neuropsychological testing, as well as the capacity to provide written and dated informed consent form. Participants were excluded from the study if they were unable/unwilling to provide consent, displayed language barriers, had current substance abuse (including nicotine, alcohol, or other substances), or did not meet the inclusion criteria.

Volunteers were screened for cognitive impairment. If they did not report SCI and the Montreal Cognitive Assessment (MoCA) [22] resulted in a score of >26, they were assigned to the *no cognitive impairment* (NCI) group. If participants reported SCI and the MoCA scored >26, they were assigned to the SCI group [26, 27]. If the MoCA resulted in a value of between 18-26 and participants reported stable cognitive function for 6 months as well as no changes in medication in the last 3 months and intact daily functions, they were assigned to the MCI group [28, 29]. After signing informed consent, eligible participants underwent neuropsychological testing, Comprehensive Geriatric Assessment (CGA) including calculation of the Multidimensional Prognostic Index (MPI) as well as blood sampling to determine plasma metabolomics, oxylipidomics and micronutrients. A dietary protocol was sent by email or regular mail in advance to the baseline visit. In addition to the filled nutritional questionnaire, participants were asked to complete the World Health Organisation's (WHO) Global Physical Activity Questionnaire (GPAQ), the European Quality of Life 5 Dimensions (EQ5D) questionnaire and the self-administered version of the MPI [30]. One year after the baseline test, participants are currently undergoing follow-up examination, in which the above-mentioned tests are performed, including blood sampling for the analyses mentioned above.

Neuropsychological tests

The Montreal Cognitive Assessment (MoCA) [28] comprises 13 tasks that test 9 cognitive domains: visuospatial abilities, executive functions, naming, memory, attention, language, abstraction, recall and orientation. Additional tests, including the trail making test A and B (TMT-A, TMT-B) [31] [25],letter fluency, and category fluency [26, 27], were performed in all participants. Executive functions were tested using TMT-B, letter fluency, and category fluency, while attention was assessed using TMT-A [32].

Comprehensive Geriatric Assessment (CGA)

The MPI can be calculated based on a CGA [33] [34]. This index is calculated by using eight elements: number of medications taken per day, living situation, comorbidities (CIRS-G) [35], the Mini Nutritional Assessment Short Form (MNA-SF) [36], activities of daily living (ADL) [37], instrumental activities of daily living (IADL) [38], Exton Smith Scale (ESS) [39], and the Short Portable Mental Status Questionnaire (SPMSQ) [40]. The MPI's mathematical algorithm delivers a continuous value between 0 and 1, that can be divided into three groups (≤0.33: robust/low risk, 0.34-0.66: pre-frail/moderate risk and ≥0.67: frail/high risk), which enables an assessment of their short- and long-term mortality among other outcomes at follow up [34]. The self-administered version of the MPI was developed as SELFY-MPI [30] and contains the Test-your-Memory (TYM) questionnaire instead than the SPSMQ and the 10 questions with several answer options from the Barthel Index instead than the ESS [30]. The Test Your Memory (TYM) is a two-sided 50-point cognitive test administered in 5 minutes and consists of 10 tasks. These cover eight cognitive domains: visuospatial abilities, executive functions, naming, language, memory, abstraction, attention, orientation.

Like the MPI, the SELFY-MPI allows a classification into three groups (≤0.33: robust/low risk, 0.34-0.66: pre-frail/moderate risk and ≥0.67: frail/high risk) [30].

Additional Assessments: Physical Activity and Quality of life

The WHO GPAQ was used to measure the participants' physical activity [41]. This self-administered questionnaire covers six categories (vigorous physical activity at work, moderate physical activity at work, physical activity during moving from place to place, vigorous physical activity during leisure time, moderate physical activity during leisure time, and sedentary behaviour) over the period of one week. These data were converted into metabolic equivalents (METs). For each minute of moderate physical activity, we estimated two METs and for each minute of vigorous physical activity, we estimated 4 METs. This was totted up and compared with the WHO recommendation of 600 METs per week [42]. To assess Patient-Reported Outcomes, the European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L) was used [43]. This brief questionnaire allows an assessment of the participants' quality of life regardless of their illnesses. It comprises five questions, each with five possible answers, which can then be converted into a score between zero (worst) and one (best). In addition, the subjective feeling of health on that day is rated on a scale from 0 (the worst imaginable state of health) to 100 (the best imaginable state of health).

Nutritional assessment

Embedded in the MPI, the MNA in its short form (MNA-SF) is the nutritional evaluation tool consisting of 6 domains, the answers to which are assigned scores from 0 to 3. It assesses weight loss, reduced food intake in the last 3 months, acute illness and severe stress in the last 3 months, as well as mobility, BMI and possible neuropsychological problems [36]. The maximum score that can be achieved is 14 points; a normal result is considered if the score is greater than or equal to 11. If the score is below 11, the index is a validated tool for diagnosis of malnutrition [36]. For the nutrient analysis, the fruit and vegetable intake of each subject was calculated in grams. The participants' diet was recorded using a paper-based food frequency questionnaire based on the “Freiburger Ernährungsprotokoll” developed by Nutri Science GmbH in 2015 [44] and has already been successfully established in previous studies to determine the nutritional status as part of the micronutrient analysis [14, 45]. This protocol categorises 157 foods and 15 beverages into 15 groups and provides a standard portion size for each. Participants recorded all foods and beverages consumed over one week, at the end of the questionnaire there was space for notes, where the participants could enter food items as free text that could not be found in the pre-prepared questionnaire. Based on this, the daily intake of energy in kilocalories and mass of macronutrients (protein, fat, carbohydrates) and alcohol in grams were calculated. 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). The amount of each food item consumed was calculated by multiplying the frequency of consumption with the portion size indicated in the questionnaire. Portion sizes of foods that were added as a note were converted to gram amounts according to the reference values used in the German health interview and examination survey for adults (Studie zur Gesundheit Erwachsener in Deutschland 1, DEGS1) [46]. The gram amounts for the food items that made up the food groups “fruits” and “vegetables” respectively were then added together.

Plasma carotenoid analysis

For the biomolecular analyses, blood was collected in both a serum tube and an EDTA tube. The serum tube was kept upright for at least 20 minutes to allow complete coagulation. Within one hour of collection, the serum sample was centrifuged for 15 minutes at 2000 times the gravitational acceleration. The resulting plasma was then divided into four vials, containing 750 µl, 500 µl, and twice 350 µl and were frozen along with the EDTA tube at minus 70 degrees Celsius. The analysis included micronutrients such as carotenoids (lutein, zeaxanthin, lycopene and β-carotene) [47, 48], vitamin A (retinol), and vitamin E (α-tocopherol); the metabolome (250 biomarkers including cholesterol, triglycerides, fatty acids, apolipoproteins, amino acids, glycolysis-related metabolites, fluid balance, inflammation, phospholipids with subclasses, and others); the oxylipidome (oxidized cholesterols, oxidised phosphatidylcholines and isoprostanes derived from eicosapentaenoic acid, arachidonic acid, docosapentaenoic acid, docosahexaenoic acid and adrenic acid) [24] and the apolipoprotein E genotype. While the metabolomics and oxylipidomic analyses as well as the follow-up visits are ongoing, the results of baseline plasma carotenoid levels are available. Carotenoid extraction and HPLC method is based on Stuetz and Weber with some modifications. Plasma (30µl) was mixed with 150µl ethanol/n-butanol (v/v 1:1) containing BHT (butylated hydroxyl toluene) and the internal standard concentration β-apo-8'-carotenal. Samples were vigorously mixed and then centrifuged to remove protein precipitates. Twenty µl of the supernatant was injected for HPLC analysis. Carotenoid analysis was carried out isocratically on Shimadzu LC 2030C Plus high-performance liquid chromatography (HPLC). All the carotenoid standards (lutein, zeaxanthin, lycopene and β-carotene, retinol, and α-tocopherol) were purchased from Cayman Chemicals, USA and HPLC grade solvents were purchased from Fisher Scientific, UK. Carotenoids were separated using a reversed phase Suplex pKb-100 HPLC Column 250x4.6 mm, 5 μm (Merck, UK). The mobile phase was 80% acetonitrile, 20% methanol and 0.05% triethylamine at a flow rate of 1 mL/min. Retinol was detected using absorption spectrum at 325nm and lutein, zeaxanthin, lycopene and β-carotene were detected at 450 nm. Emission spectrum at 325nm was used to identify α-tocopherol. Quantification of each carotenoid was performed using the Shimadzu Lab Solutions software in relation to the internal standard. Concentrations were calculated using the peak area of standard reference curves [47].

Statistics

The statistical analysis was performed using the IBM software SPSS, version 28.0. The descriptive statistics are expressed by absolute numbers and relative frequencies for categorical variables and mean values (standard deviation, SD) or median and the interquartile range (IQR) for continuous variables. The normal distribution was tested using the Kolmogorov-Smirnov test. Depending on the distribution, continuous variables were analysed by t-tests or non-parametric tests such as the Mann-Whitney U-test between two groups or by the Kruskal-Walli's test when comparing more than two groups. Rates were compared using the chi-square test or Fisher's exact test. Spearman-Rho was used for the non-parametric correlations. Similarly, linear and logistic regressions were used for the regression analyses. A P-value below 0.05 was considered significant.

RESULTS

Due to difficulties in the identification and inclusion in the MCI group, the recruitment was stopped at 125 participants, and as two NCI volunteers had to be excluded due to BMI miscalculation, 123 participants are included in the present analysis (Figure 1): 49

SCI (29 women (59.2%), 72.5 ±5.4 years), 26 MCI (9 women (34.6%), 74.5 ±5.8 years) and 50 NCI (21 women (43.8%), 70.8 ±4.3 years).

Demographic and clinical characteristics

After calculation with the Kolmogorov-Smirnov test, normal distributions were found for education years, weight, height and BMI, letter fluency tests and the micronutrients except β-carotene, lycopene and retinol. Additionally, the clock drawing time in seconds and the cube drawing time in seconds (parts of the MoCA for measuring visuospatial abilities and executive functions) as well as the metabolic equivalents based on the GPAQ were found to be normally distributed. The statistical calculations were carried out on this basis as described above.

Of the 123 participants, 59 (48.0%) were female and the average age was 72.3 years (± 5.2). Seventy-three.2% lived with family members and had an average of 18 years of education and training (±4.0). The average BMI of all participants was 24.3 (± 2.8) kg/m^2. A total of 98 participants (79.7%) had already sought advanced care planning, and 20.3% had been hospitalised in the year prior to study enrolment. The most common comorbidities were sensory impairments, e.g. visual or hearing impairments (96.7%), musculoskeletal diseases, e.g. osteoarthritis or lumbago (65.0%) and endocrinological diseases, e.g. diabetes mellitus or hypothyroidism (62.6%). On average, the participants took 3 medications daily (IQR 3), 35.0% took more than 3 medications daily. The average MPI score was 0.10 (±0.09), which corresponds to the low MPI risk group MPI-1. All participants could be assigned to the MPI-1 risk group and were considered robust, non-frail. Further demographic and clinical data of all patients are depicted in Table 1.

Demographic and clinical data of all participants: comparison of NCI – SCI – MCI

There were no statistically significant differences between groups as far as sex is concerned. With 74.5 ±5.8 years, the average age of MCI was significantly higher (p=0.022) than in SCI (72.5 ± 5.4) and NCI (70.6 ± 4.3). Accordingly, all subsequent analyses were adjusted for age and sex. There was no significant difference in the period of education (p=0.130), but more participants with SCI were living alone (42.9%) compared to the other groups (NCI 10.4% and MCI 26.9%, p=0.055). There were no differences between the groups in terms of body composition, i.e. weight, height and BMI, and comorbidities. The MPI score was highest in SCI with a mean value of 0.13 ± 0.09 (p=0.054) compared to NCI group (0.07 ± 0.08) and MCI group (0.10 ± 0.09), but all observed values were in the range of the MPI-1 group and participants could be therefore considered robust (0.00-0.33). After adjustment for age and sex, no significant differences were found between groups as far as neuropsychological tests are concerned, with the exception of MoCA scores. Further demographic features of the participants are displayed in table 1.

After adjustment for age, sex and daily fruit and vegetable intake, the micronutrient levels were significantly different between the three groups only for α-tocopherol (p=0.035) /Table 2)

Linear Regressions

All participants

As mentioned above, linear correlations were adjusted for age, sex and daily fruit and vegetable intake. There was a significant positive correlation between plasma lutein levels and the number of correct words in category fluency (b=3.65, p=0.026), which remained statistically significant after adjustment for age, sex, nutritional intake and MNA-SF (p=0.024). There was a significant negative correlation for both zeaxanthin (b=-1.79, p=0.003) and α-tocopherol (b=-0.32, p=0.009) with the CIRS-G score of the participants. Additionally, there was a significant negative correlation for zeaxanthin and the medications taken daily (b=-6.12, p=0.005). For α-tocopherol, a positive correlation with the MNA-SF was seen as well (b=0.71, p=0.010). Further linear regressions of the entire study collective are illustrated in Table 3.

DISCUSSION

With this preliminary analysis of the ongoing CogLife 2.0-study, we were able to demonstrate a significant correlation between cognitive performance and plasma lutein concentrations across the continuum from cognitive integrity to MCI in otherwise robust community dwellers. While our results are consistent with previous reports [14, 17, 45], the present observation is particularly of note due to its independency from several nutritional indicators. The lipophilic micronutrients from the carotenoid group (lutein, zeaxanthin, lycopene, β-carotene) as well as retinol (vitamin A) and α-tocopherol (vitamin E) appear to be particularly important in the prevention of dementia due to their antioxidant effects and the possibility of reducing inflammation by binding free radicals [8, 12, 17]. Carotenoids are generally regarded as robust biomarkers that can allow conclusions to be drawn about the nutrition of the participants [49]. Previous studies have already shown that lipophilic antioxidant micronutrients are significantly associated with cognitive performance and physical fitness in MCI patients [14, 45] as well as in healthy adults [49]. We could now confirm this trend in the continuum from cognitive integrity to MCI in deeply phenotypised, otherwise nonfrail community dwellers. In the MARK-Age study, higher levels of carotenoids were significantly associated with a lower risk of cognitive frailty in healthy volunteers aged 35 – 74 years [17]. In the present analysis, the association between xanthophyll components and verbal fluency, known to well discriminate between normal aging, amnestic MCI and

AD [50], was shown to be independent from nutritional status and daily fruit and vegetable intake, in addition to age and sex [24, 51]. .

Being the brain extremely susceptible to age-associated biochemical changes in the body, especially oxidative stress, RNA oxidation, accumulation of unsaturated fatty acids and neurotransmitter auto-oxidation [12], [18, 52], carotenoids, especially xanthophylls, may exert a particularly protective role on cognitive and motoric functions [12, 25]. Preferential uptake systems and the interconnections shown so far between lipophilic micronutrients and the lipidome, in addition, might be influenced by inflammaging and other aging hallmarks [11, 53]. Based on these findings, the ongoing oxylipidomics and metabolomics analyses may uncover determinant biomolecular pathways explaining to date poorly understood brain protective mechanisms of carotenoids.

The entire study cohort was highly educated (the median duration of education and training was between 18.6 and 16.8 years) and therefore health conscious, which is a typical limitation of this kind of studies. This health consciousness is also seen in participants' diet, as there were no significant differences in daily fruit and vegetable consumption between the three groups (see Table 1). However, the longitudinal nature and the intent of the study are purposefully aiming at embracing and disentangling complexity of brain aging beyond habits. Another potential limitation of the study is the small number of recruited MCI participants. However, several significant differences were found among groups and once again the profound explorative mechanistic scope of this investigation does not require large numbers typical of epidemiological studies.

In summary, this study, analogous to previous studies, underscores the importance of lipophilic micronutrients as biomarkers of cognitive performance and frailty beyond their role of nutritional indicators. For a better understanding of the cognitive functions in association with the biomarkers and the development of cognitive performance in the longitudinal course, the complete analyses of the metabolome and the oxylipidome and the completion of the 1-year follow-up of the present study are eagerly awaited.

AUTHOR CONTRIBUTIONS

Lena Pickert (Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation Writing - Original Draft, Writing - Review & Editing), Irundika HK Dias (Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Project administration), Alexander Thimm (Methodology, Formal analysis, Investigation, Data Curation), Johann Weber (Methodology, Formal analysis, Investigation, Data Curation), Sewa Abdullah (Methodology) Joris Deelen (Methodology, Writing - Review & Editing, Data Curation, Project administration), Maria Cristina Polidori (Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration)

CONFLICT OF INTEREST

M. Cristina Polidori is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review. The other authors have no conflict of interest to report.

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DATA AVAILABITIY

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

[1] St Sauver JL, Boyd CM, Grossardt BR, Bobo WV, Finney Rutten LJ, Roger VL, Ebbert JO, Therneau TM, Yawn BP, Rocca WA (2015) Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ Open* **5**, e006413.

[2] Tesar V (2022) SGLT2 inhibitors in non-diabetic kidney disease. *Adv Clin Exp Med* **31**, 105-107.

[3] Wanner C, Inzucchi SE, Zinman B (2016) Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* **375**, 1801-1802.

[4] Mosenzon O, Blicher TM, Rosenlund S, Eriksson JW, Heller S, Hels OH, Pratley R, Sathyapalan T, Desouza C, Investigators P (2019) Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. *Lancet Diabetes Endocrinol* **7**, 515-527.

[5] Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, Dent G, Hansson O, Harrison K, von Hehn C, Iwatsubo T, Mallinckrodt C, Mummery CJ, Muralidharan KK, Nestorov I, Nisenbaum L, Rajagovindan R, Skordos L, Tian Y, van Dyck CH, Vellas B, Wu S, Zhu Y, Sandrock A (2022) Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *J Prev Alzheimers Dis* **9**, 197-210.

[6] Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RYK, Lannfelt L, Bradley H, Rabe M, Koyama A, Reyderman L, Berry DA, Berry S, Gordon R, Kramer LD, Cummings JL (2021) A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Abeta protofibril antibody. *Alzheimers Res Ther* **13**, 80.

[7] Polidori MC, Nelles G, Pientka L (2010) Prevention of dementia: focus on lifestyle. *Int J Alzheimers Dis* **2010**.

[8] Townsend RF, Logan D, O'Neill RF, Prinelli F, Woodside JV, McEvoy CT (2023) Whole Dietary Patterns, Cognitive Decline and Cognitive Disorders: A Systematic Review of Prospective and Intervention Studies. *Nutrients* **15**.

[9] Mamalaki E, Charisis S, Anastasiou CA, Ntanasi E, Georgiadi K, Balomenos V, Kosmidis MH, Dardiotis E, Hadjigeorgiou G, Sakka P, Scarmeas N, Yannakoulia M (2022) The Longitudinal Association of Lifestyle with Cognitive Health and Dementia Risk: Findings from the HELIAD Study. *Nutrients* **14**.

[10] Polidori MC (2020) Physiology of Aging as a basis of complexity in aging medicine and geriatrics. In *Encyclopedia of Biogerontology and Population Aging*, Springer.

[11] Hornburg D, Wu S, Moqri M, Zhou X, Contrepois K, Bararpour N, Traber GM, Su B, Metwally AA, Avina M, Zhou W, Ubellacker JM, Mishra T, Schussler-Fiorenza Rose SM, Kavathas PB, Williams KJ, Snyder MP (2023) Dynamic lipidome alterations associated with human health, disease and ageing. *Nat Metab* **5**, 1578-1594.

[12] Polidori MC, Stahl W, Griffiths HR (2021) Nutritional cognitive neuroscience of aging: Focus on carotenoids and cognitive frailty. *Redox Biol* **44**, 101996.

[13] Rattan SIS, Kaur G (2022) Nutrition, Food and Diet in Health and Longevity: We Eat What We Are. *Nutrients* **14**.

[14] Gerger P, Pai RK, Stuckenschneider T, Falkenreck J, Weigert H, Stahl W, Weber B, Nelles G, Spazzafumo L, Schneider S, Polidori MC (2019) Associations of Lipophilic Micronutrients with Physical and Cognitive Fitness in Persons with Mild Cognitive Impairment. *Nutrients* **11**.

[15] Lorenzo-Lopez L, Maseda A, de Labra C, Regueiro-Folgueira L, Rodriguez-Villamil JL, Millan-Calenti JC (2017) Nutritional determinants of frailty in older adults: A systematic review. *BMC Geriatr* **17**, 108.

[16] Polidori MC, Carrillo JC, Verde PE, Sies H, Siegrist J, Stahl W (2009) Plasma micronutrient status is improved after a 3-month dietary intervention with 5 daily portions of fruits and vegetables: implications for optimal antioxidant levels. *Nutr J* **8**, 10.

[17] Rietman ML, Spijkerman AMW, Wong A, van Steeg H, Burkle A, Moreno-Villanueva M, Sindlinger T, Franceschi C, Grubeck-Loebenstein B, Bernhardt J, Slagboom PE, Toussaint O, Debacq-Chainiaux F, Sikora E, Gonos ES, Breusing N, Stuetz W, Weber D, Grune T, Basso A, Piacenza F, Malavolta M, Collino S, Jansen E, Verschuren WMM, Dolle MET (2019) Antioxidants linked with physical, cognitive and psychological frailty: Analysis of candidate biomarkers and markers derived from the MARK-AGE study. *Mech Ageing Dev* **177**, 135-143.

[18] Rinaldi P, Polidori MC, Metastasio A, Mariani E, Mattioli P, Cherubini A, Catani M, Cecchetti R, Senin U, Mecocci P (2003) Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. *Neurobiol Aging* **24**, 915-919.

[19] Sies H, Belousov VV, Chandel NS, Davies MJ, Jones DP, Mann GE, Murphy MP, Yamamoto M, Winterbourn C (2022) Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. *Nat Rev Mol Cell Biol* **23**, 499-515.

[20] Kao YC, Ho PC, Tu YK, Jou IM, Tsai KJ (2020) Lipids and Alzheimer's Disease. *Int J Mol Sci* **21**.

[21] Dias IHK, Milic I, Heiss C, Ademowo OS, Polidori MC, Devitt A, Griffiths HR (2020) Inflammation, Lipid (Per)oxidation, and Redox Regulation. *Antioxid Redox Signal* **33**, 166-190.

[22] Dias IHK, Milic I, Lip GYH, Devitt A, Polidori MC, Griffiths HR (2018) Simvastatin reduces circulating oxysterol levels in men with hypercholesterolaemia. *Redox Biol* **16**, 139-145.

[23] Dias HK, Brown CL, Polidori MC, Lip GY, Griffiths HR (2015) LDL-lipids from patients with hypercholesterolaemia and Alzheimer's disease are inflammatory to microvascular endothelial cells: mitigation by statin intervention. *Clin Sci (Lond)* **129**, 1195-1206.

[24] Dias IH, Polidori MC, Li L, Weber D, Stahl W, Nelles G, Grune T, Griffiths HR (2014) Plasma levels of HDL and carotenoids are lower in dementia patients with vascular comorbidities. *J Alzheimers Dis* **40**, 399-408.

[25] Polidori MC (2024) Embracing complexity of (brain) aging *FEBS Women in Science Lecture* **In press**.

[26] Rabin LA, Smart CM, Crane PK, Amariglio RE, Berman LM, Boada M, Buckley RF, Chetelat G, Dubois B, Ellis KA, Gifford KA, Jefferson AL, Jessen F, Katz MJ, Lipton RB, Luck T, Maruff P, Mielke MM, Molinuevo JL, Naeem F, Perrotin A, Petersen RC, Rami L, Reisberg B, Rentz DM, Riedel-Heller SG, Risacher SL, Rodriguez O, Sachdev PS, Saykin AJ, Slavin MJ, Snitz BE, Sperling RA, Tandetnik C, van der Flier WM, Wagner M, Wolfsgruber S, Sikkes SA (2015) Subjective Cognitive Decline in Older Adults: An Overview of Self-Report Measures Used Across 19 International Research Studies. *J Alzheimers Dis* **48 Suppl 1**, S63-86.

[27] Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chetelat G, Dubois B, Dufouil C, Ellis KA, van der Flier WM, Glodzik L, van Harten AC, de Leon MJ, McHugh P, Mielke MM, Molinuevo JL, Mosconi L, Osorio RS, Perrotin A, Petersen RC, Rabin LA, Rami L, Reisberg B, Rentz DM, Sachdev PS, de la Sayette V, Saykin AJ, Scheltens P, Shulman MB, Slavin MJ, Sperling RA, Stewart R, Uspenskaya O, Vellas B, Visser PJ, Wagner M, Subjective Cognitive Decline Initiative Working G (2014) A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement* **10**, 844-852.

[28] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.

[29] Stuckenschneider T, Sanders ML, Devenney KE, Aaronson JA, Abeln V, Claassen J, Guinan E, Lawlor B, Meeusen R, Montag C, Olde Rikkert MGM, Polidori MC, Reuter M, Schulz RJ, Vogt T, Weber B, Kessels RPC, Schneider S (2020) NeuroExercise: The Effect of a 12-Month Exercise Intervention on Cognition in Mild Cognitive Impairment-A Multicenter Randomized Controlled Trial. *Front Aging Neurosci* **12**, 621947.

[30] Cella A, Ferrari A, Rengo G, Solfrizzi V, Veronese N, Puntoni M, Zora S, Pilotto A, Fimognari F, Investigators S-MS (2020) Agreement of a Short Form of the Self-Administered Multidimensional Prognostic Index (SELFY-MPI-SF): A Useful Tool for the Self-Assessment of Frailty in Community-Dwelling Older People. *Clin Interv Aging* **15**, 493-499.

[31] Tombaugh TN (2004) Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol* **19**, 203-214.

[32] Reitan RM (1955) The relation of the trail making test to organic brain damage. *J Consult Psychol* **19**, 393-394.

[33] Rubenstein LZ, Stuck AE, Siu AL, Wieland D (1991) Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. *J Am Geriatr Soc* **39**, 8S-16S; discussion 17S-18S.

[34] Pilotto A, Sancarlo D, Panza F, Paris F, D'Onofrio G, Cascavilla L, Addante F, Seripa D, Solfrizzi V, Dallapiccola B, Franceschi M, Ferrucci L (2009) The Multidimensional Prognostic Index (MPI), based on a comprehensive geriatric assessment predicts short- and long-term mortality in hospitalized older patients with dementia. *J Alzheimers Dis* **18**, 191-199.
[35] Salvi F, Miller MD, Grilli A, Giorgi R, Towers AL, Morichi V, Spazzafumo L, Mancinelli L, Espinosa E, Rappelli A, Dessi-Fulgheri P (2008) A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc* **56**, 1926-1931.
[36] Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B (2001) Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci* **56**, M366-372.
[37] Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW (1963) Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. *JAMA* **185**, 914-919.
[38] Lawton MP, Brody EM (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179-186.
[39] Bliss MR, McLaren R, Exton-Smith AN (1966) Mattresses for preventing pressure sores in geriatric patients. *Mon Bull Minist Health Public Health Lab Serv* **25**, 238-268.
[40] Pfeiffer E (1975) A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* **23**, 433-441.
[41] World Health Organization, Global physical activity questionnaire (GPAQ), https://www.who.int/publications/m/item/global-physical-activity-questionnaire, 13.11.2021, Accessed 28.04.2024.
[42] Chu AH, Ng SH, Koh D, Muller-Riemenschneider F (2015) Reliability and Validity of the Self- and Interviewer-Administered Versions of the Global Physical Activity Questionnaire (GPAQ). *PLoS One* **10**, e0136944.
[43] Ludwig K, Graf von der Schulenburg JM, Greiner W (2018) German Value Set for the EQ-5D-5L. *Pharmacoeconomics* **36**, 663-674.
[44] Das Deutsche Ernährungsberatungs- und -informationsnetz (DEBInet), Freiburger Ernährungsprotokoll, https://www.ernaehrung.de/static/pdf/freiburger-ernaehrungsprotokoll.pdf, Accessed 28.04.2024.
[45] Weigert H, Stuckenschneider T, Pickert L, Rossi A, Meyer AM, Nelles G, Schulz RJ, Stahl W, Schneider S, Polidori MC, NeuroExercise Study G (2022) Influence of a 12-Month Structured Exercise Program on the Micronutrient-Cognitive Fitness-Physical Association Profiles in Mild Cognitive Impairment. *J Alzheimers Dis Rep* **6**, 711-722.
[46] Scheidt-Nave C, Kamtsiuris P, Gosswald A, Holling H, Lange M, Busch MA, Dahm S, Dolle R, Ellert U, Fuchs J, Hapke U, Heidemann C, Knopf H, Laussmann D, Mensink GB, Neuhauser H, Richter A, Sass AC, Rosario AS, Stolzenberg H, Thamm M, Kurth BM (2012) German health interview and examination survey for adults (DEGS) - design, objectives and implementation of the first data collection wave. *BMC Public Health* **12**, 730.
[47] Aust O, Sies H, Stahl W, Polidori MC (2001) Analysis of lipophilic antioxidants in human serum and tissues: tocopherols and carotenoids. *J Chromatogr A* **936**, 83-93.
[48] Bohm V, Lietz G, Olmedilla-Alonso B, Phelan D, Reboul E, Banati D, Borel P, Corte-Real J, de Lera AR, Desmarchelier C, Dulinska-Litewka J, Landrier JF, Milisav I, Nolan J, Porrini M, Riso P, Roob JM, Valanou E, Wawrzyniak A, Winklhofer-Roob BM, Ruhl R, Bohn T (2021) From carotenoid intake to carotenoid blood and tissue concentrations - implications for dietary intake recommendations. *Nutr Rev* **79**, 544-573.
[49] Polidori MC, Pratico D, Mangialasche F, Mariani E, Aust O, Anlasik T, Mang N, Pientka L, Stahl W, Sies H, Mecocci P, Nelles G (2009) High fruit and vegetable intake is positively correlated with antioxidant status and cognitive performance in healthy subjects. *J Alzheimers Dis* **17**, 921-927.
[50] McDonnell M, Dill L, Panos S, Amano S, Brown W, Giurgius S, Small G, Miller K (2020) Verbal fluency as a screening tool for mild cognitive impairment. *Int Psychogeriatr* **32**, 1055-1062.
[51] Polidori MC, Stahl W, De Spirt S, Pientka L (2012) [Influence of vascular comorbidities on the antioxidant defense system in Alzheimer's disease]. *Dtsch Med Wochenschr* **137**, 305-308.
[52] Mangialasche F, Baglioni M, Cecchetti R, Kivipelto M, Ruggiero C, Piobbico D, Kussmaul L, Monastero R, Brancorsini S, Mecocci P (2015) Lymphocytic mitochondrial aconitase activity is reduced in Alzheimer's disease and mild cognitive impairment. *J Alzheimers Dis* **44**, 649-660.
[53] Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A (2018) Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* **14**, 576-590.

Table 1: Demographical and clinical data for all participants

	All patients (n= 123)	NCI (no cognitive impairment) (n=48, 39.0%)	SCI (subjective cognitive impairment) (n=49, 39.8%)	MCI (mild cognitive impairment) (n= 26, 21.1%)	p-value°
Female, *n (%)*	59 (48)	21 (43.8)	29 (59.2)	9 (34.6)	0.097
Age at recruitment (years), *mean (SD)*	72.25 (5.24)	70.8 (4.34)	72.5 (5.36)	74.5 (5.80)	**0.022**
Living conditions, *n (%)* Alone With family/relatives	 33 (26.8) 90 (73.2)	 5 (10.4) 43 (89.6)	 21 (42.9) 28 (57.1)	 7 (26.9) 19 (73.1)	0.055
Period of education (years), *mean (SD)*	18.07 (3.96)	18.6 (4.10)	18.2 (3.81)	16.8 (3.85)	0.130
Medical history					
Hospitalisation in the last 12 months, *n (%)*	25 (20.3)	9 (18.8)	10 (20.4)	6 (23.1)	0.906
Falls in the last 12 months, *n (%)*	12 (9.8)	2 (4.2)	6 (12.2)	4 (15.4)	0.089
Advanced care planning, *n (%)*	98 (79.7)	42 (87.5)	37 (75.5)	19 (73.1)	0.081
Taking more than 3 drugs per day, *n (%)*	43 (35)	14 (29.2)	21 (42.9)	8 (30.8)	0.747
Comorbidities					
Heart disease, *n (%)*	37 (30.1)	14 (29.2)	15 (30.6)	8 (30.8)	0.585
Hypertension, *n (%)*	64 (52)	24 (50)	26 (53.1)	14 (53.8)	0.849
Vascular/Blood /Lymphatic Disease, *n (%)*	39 (31.7)	18 (37.5)	11 (22.4)	10 (38.5)	0.665
Respiratory disease, *n (%)*	20 (16.3)	7 (14.6)	8 (16.3)	5 (19.2)	0.464
Diseases of the sensory organs, *n (%)*	119 (96.7)	47 (97.9)	48 (98)	24 (92.3)	0.392
Diseases of the upper GI tract, *n (%)*	36 (29.3)	14 (29.2)	15 (30.6)	7 (26.9)	0.741
Diseases of the lower GI tract, *n (%)*	22 (17.9)	8 (16.7)	10 (20.4)	4 (15.4)	0.989
Liver disease, *n (%)*	13 (10.6)	6 (12.5)	4 (8.2)	3 (11.5)	0.984
Kidney disease, *n (%)*	9 (7.3)	4 (8.3)	4 (8.2)	1 (3.8)	0.487
Diseases of the urogenital tract, *n (%)*	55 (44.7)	21 (43.8)	22 (44.9)	12 (46.2)	0.791
Musculoskeletal diseases, *n (%)*	80 (65)	27 (56.3)	33 (67.3)	20 (76.9)	0.086
Neurological diseases, *n (%)*	24 (19.5)	7 (14.6)	10 (20.4)	7 (26.9)	0.282
Endocrinological diseases, *n (%)*	77 (62.6)	28 (58.3)	36 (73.5)	13 (50.0)	0.719
Psychiatric disorders, *n (%)*	59 (48)	13 (27.1)	34 (69.4)	12 (46.2)	**0.020**
Nutritional status					
Weight (in kilogram), *mean (SD)*	72.43 (12.34)	74.7 (12.36)	70.4 (11.87)	72.0 (12.91)	0.380
Height (in centimetres), *mean (SD)*	172.28 (8.85)	173.2 (8.99)	170.9 (8.78)	173.2 (8.70)	0.720
Body mass index (BMI) in kg/m^2, *mean (SD)*	24.27 (2.76)	24.80 (2.81)	23.98 (2.73)	23.85 (2.69)	0.409
Fruit and vegetable intake per day (in gram), median (IQR)	455.83 (341.43)	455.83 (377.14)	457.50 (281.67)	445.00 (396.50)	0.837
Mobility and activity					
GPAQ WHO Recommendations met: yes *n (%) (n= 119)*	112 (94.1)	44 (95.7)	44 (91.7)	24 (96.0)	0.709
GPAQ WHO MET (minutes), *median (IQR) (n= 119 total)*	3600 (4520)	3280 (4920)	3840 (4200)	3660 (4883)	0.971
GPAQ WHO sitting (minutes), *median (IQR) (n= 116 total)*	1680 (2100)	2310 (1920)	1470 (2130)	1260 (1770)	**0.016**
Multidimensional Prognostic Index (MPI)					
ADL, *median (IQR)*	6 (0)	6 (0)	6 (0)	6 (0)	0.324
IADL, *median (IQR)*	8 (0)	8 (0)	8 (0)	8 (0)	**0.025**
MNA-SF, *median (IQR)*	13 (2)	13 (2)	13 (2)	14 (2)	0.519
SPMSQ, *median (IQR)*	0 (0)	0 (0)	0 (0)	0 (0)	0.312
ESS, *median (IQR)*	20 (0)	20 (0)	20 (0)	20 (1)	0.486
CIRS-G, *median (IQR)*	0 (1)	0 (1)	1 (1)	0 (1)	0.455
Medications taken daily, *median (IQR)*	3 (3)	2 (3)	3 (4)	3 (2)	0.692
MPI, *mean (SD)*	0.10 (0.09)	0.07 (0.08)	0.13 (0.09)	0.10 (0.09)	0.054
SELFY-MPI score, *median (IQR) (n= 93 total)*	0.19 (0.13)	0.13 (0.14)	0.25 (0.13)	0.19 (0.13)	0.068
Neuropsychological tests					
Montreal Cognitive Assessment, *median (IQR)*	27 (3)	28 (2)	28 (2)	24 (2)	**<0.001**
TMT-A in seconds, *median (IQR)*	35 (16.9)	34 (14.6)	33 (16.8)	42 (21.8)	0.094
TMT-B in seconds, *median (IQR) (n= 119 total)*	87 (51)	73 (52)	86 (50.2)	90.5 (46.3)	0.103

Letter fluency (L), *mean (SD)*	13.9 (4.5)	13.3 (4.0)	14.0 (3.9)	14.5 (4.4)	0.596
Letter fluency (B), *mean (SD)*	15.3 (4.7)	14.8 (4.5)	15.6 (5.1)	14.4 (3.4)	0.261
Letter fluency (S), *mean (SD)*	16.6 (4.9)	16.6 (3.9)	17.2 (6.0)	15.8 (5.3)	0.144
Category fluency (animals), *mean (SD)*	22.6 (4.6)	22.6 (3.5)	22.8 (4.4)	20.3 (3.8)	0.139
Test your memory, *median (IQR)* *(n= 122 total)*	49 (3)	49 (2)	49 (3)	47 (4)	**0.010**
Quality of life					
Mobility *(n= 117), n (%)*					0.854
No problems	110 (94.0)	44 (95.7)	43 (91.5)	23 (95.8)	
Minor problems	4 (3.4)	1 (2.2)	1 (4.3)	1 (4.2)	
Moderate problems	3 (2.6)	1 (2.2)	2 (4.3)	0 (0.0)	
Severe problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Selfcare *(n= 117), n (%)*					0.473
No problems	116 (99.1)	46 (100)	46 (97.9)	24 (100)	
Minor problems	1 (0.9)	0 (0.0)	1 (2.1)	0 (0.0)	
Moderate problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Severe problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Activities of daily living (*n= 116), n (%)*					0.600
No problems	113 (97.4)	45 (97.8)	45 (97.8)	23 (95.8)	
Minor problems	3 (2.6)	1 (2.2)	1 (2.2)	1 (4.2)	
Moderate problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Severe problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Pain *(n= 116), n (%)*					**0.050**
No problems	59 (50.9)	28 (60.9)	19 (41.3)	12 (50.0)	
Minor problems	47 (40.5)	15 (32.6)	24 (52.2)	8 (33.3)	
Moderate problems	8 (6.9)	3 (6.5)	2 (4.3)	3 (12.5)	
Severe problems	2 (1.7)	0 (0.0)	1 (2.2)	1 (4.2)	
Fear/Depression *(n= 116), n (%)*					0.605
No problems	102 (87.9)	42 (91.3)	39 (84.8)	21 (87.5)	
Minor problems	14 (12.1)	4 (8.7)	7 (15.2)	3 (12.5)	
Moderate problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Severe problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Visual analog scale *(n=116), median (IQR)*	90 (11)	90 (10)	87 (10)	85 (10)	0.116

Table 1 Subtitle: Demographic and clinical data of baseline characteristics for all patients and divided into no cognitive impairment (NCI), subjective cognitive impairment (SCI) and mild cognitive impairment (MCI), p-value significant when $p<0.05$. Abbreviations: standard deviation (SD), interquartile range (IQR), gastrointestinal (GI), trail-making-test A/B (TMT A/B), Activities of daily living (ADL), Instrumental Activities of daily living (IADL), Mini nutritional assessment – short form (MNA-SF), Exton-Smith-Scale (ESS), Cumulative Illness Rating Scale-Geriatric (CIRS-G), Multidimensional Prognostic Index (MPI), World Health Organisation's (WHO) Global Physical Activity Questionnaire (GPAQ), metabolic equivalent . °p-value adjusted for age and sex

Table 2: Micronutrients

	All patients (n= 111)	NCI (no cognitive impairment) (n=43, 38.7%)	SCI (subjective cognitive impairment) (n=47, 42.3%)	MCI (mild cognitive impairment) (n= 21, 18.9%)	p-value°
Micronutrients					
Lutein (in µmol/l), *mean (SD)*	0.70 (0.25)	0.66 (0.21)	0.72 (0.25)	0.72 (0.33)	0.405
Zeaxanthin (in µmol/l), *mean (SD)*	0.16 (0.11)	0.15 (0.08)	0.15 (0.09)	0.21 (0.17)	0.057
Lycopene (in µmol/l), *median (IQR))*	0.84 (0.52)	0.72 (0.53)	0.87 (0.56)	0.89 (0.55)	0.080
β-caroten (in µmol/l), *median (IQR)*	0.70 (0.56)	0.69 (0.59)	0.82 (0.62)	0.49 (0.53)	0.595
α-tocopherol (in µmol/l), *mean (SD)*	2.94 (0.59)	2.80 (0.58)	2.99 (0.62)	3.09 (0.53)	**0.035**
Retinol (in µmol/l), *median (IQR)*	1.12 (0.29)	1.11 (0.28)	1.17 (0.27)	1.08 (0.33)	0.480

<u>Table 2 Subtitle:</u> Demographic and clinical data of baseline characteristics for all patients and divided into no cognitive impairment (NCI), subjective cognitive impairment (SCI) and mild cognitive impairment (MCI), p-value significant when p<0.05. Abbreviations: standard deviation (SD), interquartile range (IQR). °p-value adjusted for age, sex and nutrition intake

Table 3: Linear regressions (adjusted for age, sex and daily fruit and vegetable intake) including all participants (only for p <0,1)

Items of the Multidimensional Prognostic Index (MPI)		b	SE	p-value	**Micronutrients**		b	SE	p-value
IADL	MoCA	1.72	0.71	0.018	Lutein	Category fluency (animals)	3.65	1.61	0.026
	TMT-A in seconds	-9.20	4.67	0.051		Medications taken daily	-1.60	0.94	0.092
	TMT-B in seconds	-35.34	13.61	0.011	Zeaxanthin	TMT-B in seconds	-61.46	36.15	0.092
	Test your memory	3.21	0.76	<0.001		Category fluency (animals)	6.32	3.79	0.098
SPMSQ	Test your memory	-1.51	0.76	0.049		Test your memory	-3.67	2.09	0.082
ESS	Category fluency (animals)	-1.62	0.75	0.033		CIRS-G score	-1.79	0.58	0.003
	Test your memory	1.07	0.41	0.011		Medications taken daily	-6.12	2.13	0.005
CIRS-G score	TMT-A in seconds	4.52	1.91	0.020		MPI score	-0.15	0.08	0.059
Medications taken daily	TMT-A in seconds	1.45	0.52	0.006	Lycopene	MoCA	-1.08	0.39	0.007
	TMT-B in seconds	2.95	1.59	0.066		TMT-A in seconds	4.72	2.62	0.074

	Category fluency (animals)	-0.30	0.17	0.069		TMT-B in seconds	22.91	7.55	0.003
						Letter fluency (B)	-2.22	0.84	0.009
						Category fluency (animals)	-1.51	0.82	0.068
						ADL	-0.09	0.05	0.051
					β-carotene	SPMSQ	-0.08	0.05	0.091
						ESS	0.17	0.09	0.057
					α-tocopherol	MNA-SF	0.71	0.27	0.010
						CIRS-G score	-0.32	0.12	0.009
						MPI score	-0.03	0.02	0.069
						SELFY-MPI score	-0.03	0.02	0.051
					Retinol	Letter fluency (F)	3.58	2.09	0.093
						ADL	-0.19	0.10	0.044

Subtitle Table 3: Regression statistics of the baseline data for all patients adjusted for age, sex and nutrition intake, p-value significant when $p<0.05$. Abbreviations: regression coefficient (b), standard error (SE), trail-making-test A/B (TMT A/B), Activities of daily living (ADL), Instrumental Activities of daily living (IADL), Mini nutritional assessment – short form (MNA-SF), Short Portable Mental Status Questionnaire (SPMSQ), Exton-Smith-Scale (ESS), Cumulative Illness Rating Scale - Geriatric (CIRS-G), Multidimensional Prognostic Index (MPI)

Figure 1: Flow-chart CogLife 2.0

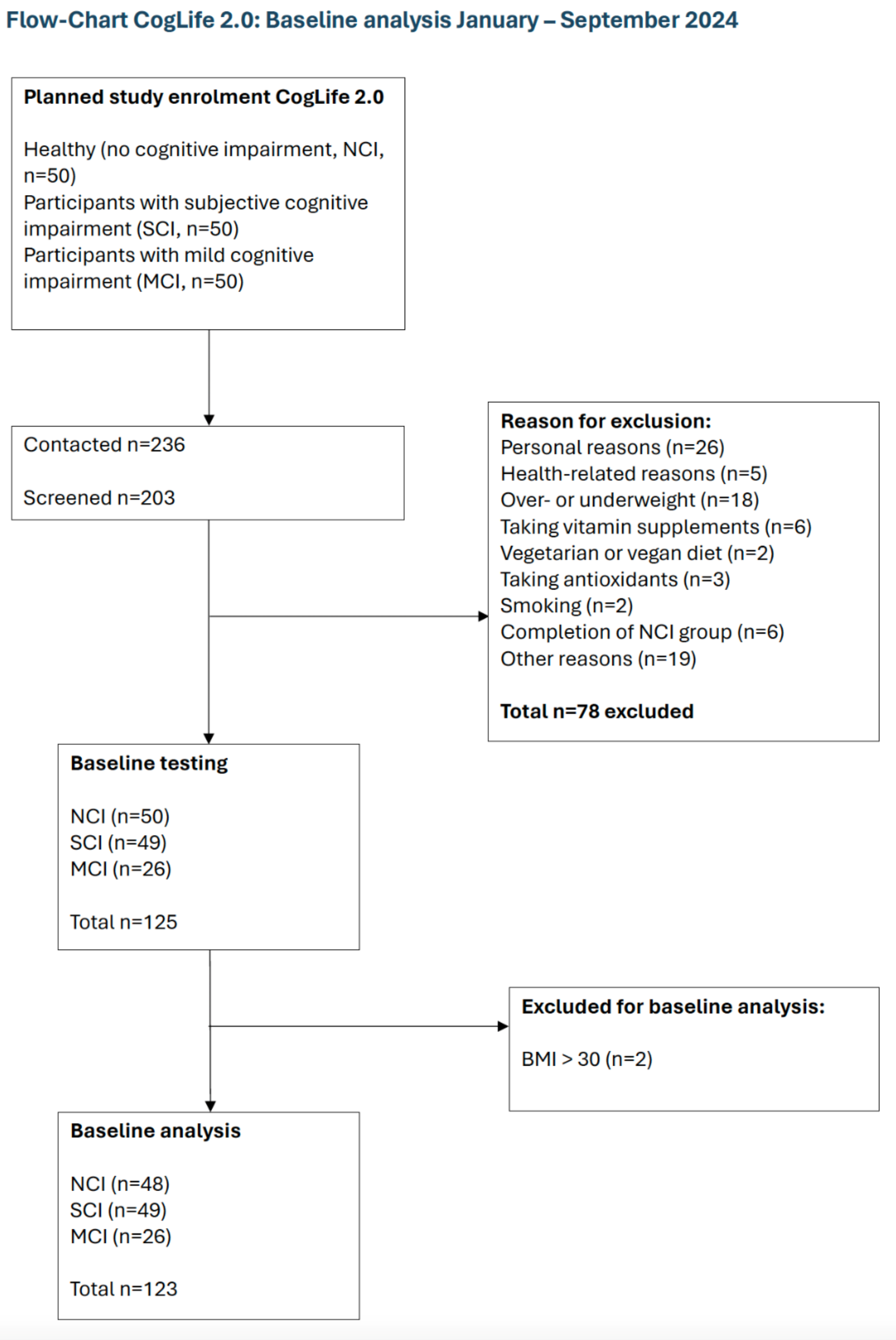

Figure 1 subtitle: The initial plan was to include 150 participants. To achieve this, 236 possible candidates were contacted, 203 of whom agreed to participate in the study after the initial expression of interest. After screening these 203, 78 were excluded for the reasons listed and 125 were included in the study. 2 participants had to be subsequently excluded from the analysis due to too high Body Mass Index (BMI). The present analysis is therefore based on data from 123 participants.