JAMDA xxx (2020) 1–7

JAMDA

journal homepage: www.jamda.com

Original Study

Nutritional Status Is Associated With Clinical Progression in Alzheimer's Disease: The NUDAD Project

Astrid S. Doorduijn MSc [a,b,*], Marian A.E. de van der Schueren PhD [c,d], Ondine van de Rest PhD [d], Francisca A. de Leeuw MD [b,e], Heleen M.A. Hendriksen MSc [b], Charlotte E. Teunissen PhD [e], Philip Scheltens MD, PhD [b], Wiesje M. van der Flier PhD [b,f], Marjolein Visser PhD [g]

[a] *Department of Nutrition and Dietetics, Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands*
[b] *Department of Neurology, Amsterdam Neuroscience, Alzheimer Center Amsterdam, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands*
[c] *Department of Nutrition and Health, School of Allied Health, HAN University of Applied Sciences, Nijmegen, the Netherlands*
[d] *Division of Human Nutrition and Health, Wageningen University and Research, Wageningen, the Netherlands*
[e] *Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands*
[f] *Department of Epidemiology & Biostatistics, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands*
[g] *Faculty of Science, Department of Health Sciences, Vrije Universiteit Amsterdam and the Amsterdam Public Health Research Institute, Amsterdam, the Netherlands*

Keywords:
Malnutrition
food intake
dementia
mild cognitive impairment
subjective cognitive decline

A B S T R A C T

Objective: In cognitively normal adults, nutritional parameters are related to cognitive decline and incidence of dementia. Studies on the role of nutrition in predementia stages subjective cognitive decline and mild cognitive impairment, and mild stages of Alzheimer's disease (AD) dementia in a clinical setting are lacking. In the absence of a curative treatment, this evidence is important for targeting nutritional factors to potentially prevent or delay further cognitive decline. Our aim is to investigate associations of nutritional parameters with clinical progression in patients ranging from those who are cognitively normal to those who have AD dementia.
Design: Longitudinal.
Setting and Participants: Memory clinic, 551 patients (219 with subjective cognitive decline, 135 with mild cognitive impairment, and 197 with AD dementia), mean age 64 ± 8 years.
Measurements: We assessed body mass index, fat-free mass, Mini-Nutritional Assessment, and dietary intake with the Dutch Healthy Diet food frequency questionnaire and the 238-item healthy life in an urban setting (HELIUS) food frequency questionnaire at baseline. Cox proportional hazard models were used to evaluate associations of nutritional parameters with clinical progression. Additional analyses were restricted to patients who were amyloid positive.
Results: We observed clinical progression in 170 patients (31%) over 2.2 ± 0.9 years. Poorer Mini-Nutritional Assessment score [hazard ratio (95% confidence interval) 1.39 (1.18−1.64)], lower body

The NUDAD project is funded by NWO-FCB (project number 057-14-004) and AD, FdL and HH are appointed on this project.
The sponsors had no role in the design, methods, participant recruitment, data collections, analysis, and preparation of the report.
AD, MdvdS, OvdR, FdL, HH, and MV have no potential conflicts of interest.
PS has served as consultant for Wyeth-Elan, Genentech, Danone, and Novartis. CT is a member of the Innogenetics International Advisory Boards of Fujirebio/Innogenetics and Roche. Research programs of WvdF have been funded by ZonMw, NWO, EU-FP7, EU-JPND, Alzheimer Nederland, CardioVascular Onderzoek Nederland, Health ~ Holland, Topsector Life Sciences and Health, stitching Dioraphte, Gieskes-Strijbis fonds, stichting Equilibrio, Pasman stichting, Biogen MA Inc, Boehringer Ingelheim, Life-MI, AVID, Roche BV, Janssen Stellar, Combinostics. WvdF has performed contract research for Biogen MA Inc and Boehringer Ingelheim. WvdF has been an invited speaker at Boehringer Ingelheim and Biogen MA Inc. All funding was paid to her institution.
Research of the Alzheimer Center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience. The Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting VUmc fonds. The clinical database structure was developed with funding from Stichting Dioraphte. WvdF holds the Pasman chair. WvdF is recipient of a NWO-FCB grant for the NUDAD project (#057-14-004). The NUDAD project is funded by NWO-FCB (project number 057-14-004) and AD, FdL and HH are appointed on this project. WvdF is recipient of a donation by stichting Equilibrio, and of a ZonMW Memorabel grant (#733050814).
* Address correspondence to Astrid S. Doorduijn, MSc, Department of Nutrition and Dietetics, Amsterdam UMC, PO Box 7057, 1007 MB Amsterdam, the Netherlands.
E-mail address: astrid.doorduijn@hotmail.com (A.S. Doorduijn).

https://doi.org/10.1016/j.jamda.2020.10.020

mass index [1.15 (0.96–1.38)], lower fat-free mass [1.40 (0.93–2.10)], and a less healthy dietary pattern [1.22 (1.01–1.48)] were associated with a higher risk of clinical progression. Similar effect sizes were found in patients who were amyloid positive.

Conclusions and Implications: Poorer nutritional status and a less healthy dietary pattern are associated with a higher risk of clinical progression. This study provides support for investigating whether improving nutritional status can alter the clinical trajectory of AD.

Studies in cognitively normal samples show that nutritional parameters are related to cognitive decline and incidence of dementia.[1] Weight loss often precedes the onset of Alzheimer's disease (AD) dementia[2–6] and older adults with poorer nutritional status [ie, lower body mass index (BMI)] show more cognitive decline and have a higher risk of dementia.[7,8] Moreover, dietary intake has been related to cognition [eg, a dietary pattern with relatively high caloric intake from carbohydrates and low caloric intake from fat and proteins may increase the risk of mild cognitive impairment (MCI) or dementia in older adults].[9] Furthermore, a healthier dietary pattern with higher intakes of fruit and vegetables has been associated with less cognitive decline and a lower risk of MCI and AD dementia.[10–14]

Fewer studies on the role of nutrition in predementia and mild stages of AD have been performed in a clinical setting. In the absence of a curative treatment, this evidence is important for targeting nutritional factors to potentially prevent or delay further cognitive decline. Three studies have shown that malnourished patients with AD dementia show a steeper rate of cognitive decline and clinical progression within 1 year compared with those with a normal nutritional status.[15–17] Furthermore, low baseline BMI has been associated with clinical progression over 1 or 2 years in patients with MCI.[18–20] One study in patients with MCI suggests that poorer adherence to the Mediterranean dietary pattern was associated with a higher risk of progression to AD dementia.[21] These previous studies focused on MCI or AD dementia, and did not take into account patients with subjective cognitive decline, who may be in the earliest stages of AD. Therefore, we investigated the associations of nutritional status as well as dietary intake with clinical progression in a memory clinic cohort of patients with subjective cognitive decline (SCD), MCI, and AD dementia.

Methods

Patients

The Nutrition, the unrecognized determinant in Alzheimer's disease (NUDAD) study is a prospective cohort study on nutritional determinants of disease progression in the clinical continuum of AD. NUDAD is a subsample of the Amsterdam Dementia Cohort, existing of patients who visited our Alzheimer center between September 2015 and August 2017 and were diagnosed with AD, MCI, or SCD and had a Mini-Mental State Examination (MMSE) score of >16.[22,23] All patients underwent standardized dementia screening, including general medical examination, extensive neuropsychological assessment, magnetic resonance imaging, and laboratory tests.[24] Patients with SCD presented with memory complaints but performed normal on all clinical and cognitive examinations (ie, did not meet the criteria for MCI, dementia, or any psychiatric diagnosis).[25] MCI and probable AD were diagnosed according to the core clinical criteria of the National Institute on Aging-Alzheimer's Association criteria.[26,27] Informed consent was obtained from all patients and the local Medical Ethics Committee approved the study. For the current study, we excluded 1 patient whose initial diagnosis of AD was retracted after 3 months, leaving 551 patients for analysis, 219 with SCD, 135 with MCI, and 197 with AD dementia. Descriptive characteristics included baseline age, sex, and MMSE score.

Clinical Progression

At annual follow-up visits to our memory clinic, neuropsychological testing and medical examination were repeated, and diagnosis was re-evaluated. If a patient was unable or did not want to visit the memory clinic, a short telephone interview was performed with the patient and/or partner to report changes in diagnosis, living situation (ie, admission to nursing home), and self-reported course of cognitive symptoms (dichotomized into progressive vs stable/improved/fluctuating). Clinical progression was operationalized when at least 1 of the following 3 criteria was met: (1) progression to MCI or dementia (for patients with SCD); progression to dementia (for patients with MCI); an increase of ≥ 1 point on Clinical Dementia Rating scale (for patients with AD dementia); (2) passed away or admitted to a nursing home; or (3) self-reported progressive course of cognitive symptoms during the telephone interview. The first report of progression was used to calculate time to event. When none of the criteria was met, a patient was censored at the date of last contact. Of 25 patients (4%), we did not have any information upon follow-up, these patients were censored at baseline (time = 0).

Baseline Nutritional Parameters

At first presentation at the Alzheimer center in Amsterdam, the following nutritional parameters were assessed. Body mass index (BMI, kg/m^2) was calculated by dividing the measured body weight by the squared measured height. Fat-free mass (FFM, kg) was estimated using multifrequency bioelectrical impedance analysis (50 KHz Quadscan 4000[Bodystat, British Isles]) and the formula of Kyle.[28] Risk of malnutrition was evaluated with the Mini-Nutritional Assessment (MNA).[29] To avoid that differences in MNA score were driven by differences in cognitive performance, we excluded the item on neuropsychological problems. Scores ranged from 0 to 28 with a higher score indicating better nutritional status. Diet quality was assessed using the Dutch Healthy Diet Food Frequency Questionnaire.[30] Adherence to the Dutch guidelines for a Healthy Diet was assessed for the following components: vegetables, fruit, fibers, fish, saturated fat, trans fat, salt, and alcohol.[31] Component scores ranged from 0 (no adherence) to 10 (complete adherence), and the total diet quality ranged from 0 to 80. The healthy life in an urban setting (HELIUS) food frequency questionnaire (FFQ) was used to assess the intake of energy, protein, carbohydrate, fat and alcohol.[32] The HELIUS FFQ is a self-administrated questionnaire asking for the frequency, amount, and type of 238 food items consumed in the past month. Daily energy (kcal) and macronutrient intake in energy percentages were calculated using the Dutch food composition table 2013.[33]

Amyloid Status

Amyloid status, as determined by either positron emission tomography (PET) scans or cerebrospinal fluid (CSF) measurements, was available for 444 patients (80%; PET n = 202, CSF n = 242). Amyloid

PET scans were assessed for amyloid positivity by an experienced nuclear medicine physician.[34] CSF was obtained by lumbar puncture using a 25-gauge needle and collected in 10 mL polypropylene tubes (Sarstedt, Nümbrecht, Germany).[35] β-amyloid 42 ($A\beta_{42}$) levels were determined with sandwich Innotest ELISAs (Fujirebio, Ghent, Belgium).[36] Patients were classified as having a positive amyloid status if they had a positive amyloid PET scan or CSF $A\beta_{42}$ drift corrected values lower than 813 pg/mL.[37]

Statistical Analysis

We compared baseline characteristics and baseline nutritional parameters between patients with and without clinical progression using *t* tests and χ^2 tests where appropriate. Analyses with FFM were adjusted for body height. Time to progression was visualized and compared according to the clinical cut-off points for BMI, FFM index, MNA score, and diet quality using Kaplan-Meier curves and log-rank tests. Based on BMI, patients were classified as underweight (<70 years of age: <18.5 kg/m^2, ≥70 years of age: <20 kg/m^2), normal weight (<70 years: 18.5–24.9 kg/m^2, ≥70 years of age: 20–26.9 kg/m^2), overweight (<70 years of age: 25–29.9 kg/m^2, ≥70 years of age: 27–29.9 kg/m^2), or obese (≥30 kg/m^2).[38,39] FFM index (FFMI, kg/m^2) was calculated by dividing the FFM by the squared measured body height. Using sex-specific cut-off points FFMI was dichotomized into low (female: <14.6 kg/m^2, male: <17.6 kg/m^2) or normal (female: ≥14.6 kg/m^2, male ≥17.6 kg/m^2).[40] Because of a small number of patients with a MNA score below 15, patients were classified as malnourished/at risk of malnutrition (score <22) or well-nourished (score ≥ 22). Diet quality was classified as poor (score <53) or normal (score ≥53).[30] For each nutritional parameter, the association with time to clinical progression was tested using a Cox proportional hazards regression model. To allow comparison of the different nutritional parameters in their relationship with clinical progression, the parameters were converted into z scores using the baseline mean and standard deviation of the total study population. Furthermore, nutritional parameters were inverted; herewith hazard ratios (HRs) present the risk of clinical progression per lower SD of the nutritional parameters. The proportional hazard assumption was checked for all parameters by visual inspection of the Kaplan-Meier curves and log minus log plots, and tested by creating a time-dependent determinant; evidence of nonproportionality was not found. Associations were adjusted for age, sex, and baseline diagnosis in the total sample and adjusted for age and sex when stratified by baseline diagnosis. For each nutritional parameter, events per person-year of follow-up were calculated by dividing the sum of events by the sum of at-risk time. To evaluate whether associations were AD pathology specific, the Cox proportional hazard models were repeated restricted to amyloid positive patients only (n = 261). Two sensitivity analyses were performed for all nutritional parameters to examine to what extent alternative combinations of the criteria used for the clinical progression definition influenced the results. In a first analysis, patients who met the criterion "passed away or admitted to a nursing home" but did not meet the other criteria, were censored (n = 24). In a second analysis, patients with self-reported progression and not meeting the other 2 criteria were censored (n = 72). If self-reported progression preceded other progression criteria, time of progression was placed at that event. Significance was set at *P* value of < .05. All analyses were performed with SPSS v 22 (released 2013, IBM SPSS Statistics for Windows, Armonk, NY).

Results

Table 1 shows the baseline characteristics of the total study sample. Information from 771 follow-up visits and 264 telephone interviews were used. During follow-up, clinical progression was observed in 25 (11%) patients with SCD, 45 (33%) patients with MCI, and 100 (51%) patients with AD dementia. Patients with progression were older, had a lower baseline MMSE, and were more often amyloid positive. Furthermore, they had lower baseline BMI, FFM, and modified MNA score and consumed more energy from fat compared with patients without progression.

Figure 1 shows how nutritional parameters are related to risk of clinical progression. Cox proportional hazard models, adjusted for age, sex, and baseline diagnosis, showed that a lower BMI [HR (95% confidence interval) 1.15 (0.96–1.38)] and lower FFM [1.40 (0.93–2.10)] tended to be associated with a higher risk of progression, albeit not statistically significant (Table 2). A lower modified MNA score was statistically significant associated with a higher risk of clinical progression [1.39 (1.18–1.64)]. Furthermore, a poorer diet quality was associated with a higher risk of progression [1.22 (1.01–1.48)]. Adjusting the models of MNA and diet quality additionally for BMI or FFM (in separate models) did not change the HRs. The associations between individual components of diet quality and risk of clinical progression are shown in Supplementary Table 1. Lower fat intake was

Table 1
Baseline Characteristics of Total NUDAD Sample

	All		Stable		Progression	
	N		n		n	
Age (y)	551	64.4 ± 8.3	381	63.6 ± 8.2	170	66.4 ± 8.3*
Sex, female	551	255 (46.3)	381	175 (45.9)	170	80 (47.1)
MMSE score	551	25.8 ± 3.3	381	26.6 ± 2.9	170	24.0 ± 3.6*
Follow-up (y)	551	2.2 ± 0.9	381	2.2 ± 0.9	170	2.1 ± 0.8
Amyloid status, positive	444	261 (58.8)	308	149 (48.4)	136	112 (82.4)*
Nutritional parameters						
BMI (kg/m^2)	551	25.8 ± 4.1	381	26.2 ± 4.2	170	25.0 ± 3.9*
FFM† (kg)	432	52.8 ± 10.7	298	53.4 ± 10.6	134	51.7 ± 10.9*
MNA‡	357	24.0 ± 2.6	250	24.3 ± 2.4	107	23.3 ± 3.1*
Diet quality	357	53.9 ± 11.5	250	54.3 ± 11.4	107	53.0 ± 11.8
Energy intake (kcal/d)	218	2051 ± 601	157	2036 ± 607	61	2087 ± 590
Protein intake (EN%)	218	15.2 ± 2.6	157	15.2 ± 2.5	61	15.2 ± 2.7
Carbohydrate intake (EN%)	218	40.9 ± 6.9	157	41.0 ± 7.0	61	40.7 ± 6.6
Fat intake (EN%)	218	34.4 ± 5.5	157	33.9 ± 5.3	61	35.7 ± 5.9*
Alcohol intake (EN%)	218	9.5 ± 5.1	157	9.9 ± 5.5	61	8.4 ± 3.9

EN%, energy percentage; SD, standard deviation.
Data in mean ± SD; n (%).
*Statistically significant different from stable.
†FFM additionally adjusted for body height.
‡MNA without item on neuropsychological problems.

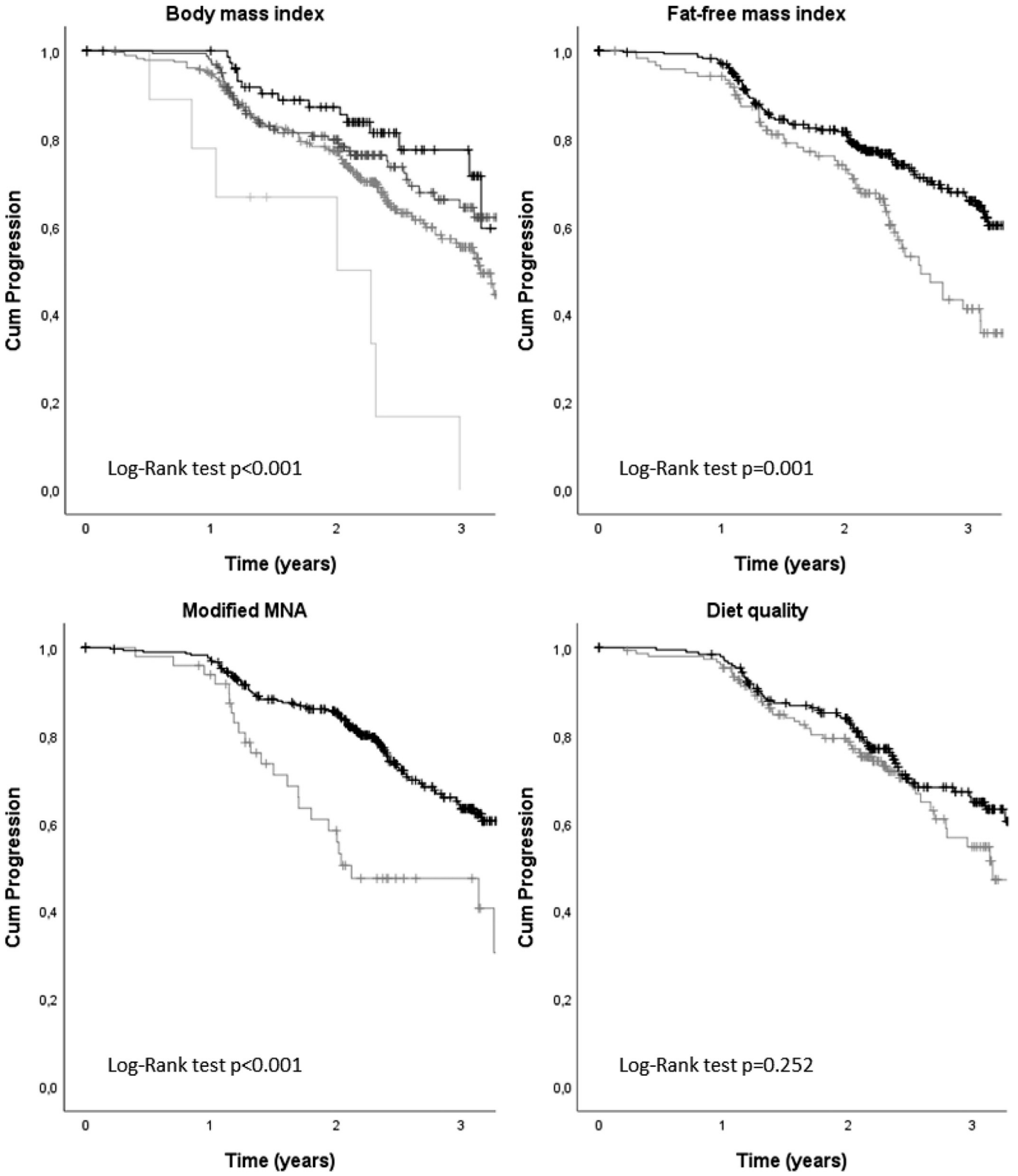

Fig. 1. Kaplan-Meier curves for progression according to parameter specific cut-off points. BMI: light gray = underweight, gray = normal weight, darkest gray = overweight, black = obese. FFM index: gray = low, black = normal. Modified MNA: gray = malnourished/risk of malnutrition, black = well-nourished. Diet quality: gray = poor, black = normal.

Table 2
Adjusted Associations Between Lower Baseline Nutritional Parameters and Clinical Progression in the Total Sample and Stratified for Baseline Diagnosis

Per SD Lower	All			SCD			MCI			AD Dementia		
	N	Events	HR (95% CI)	N	Events	HR (95% CI)	N	Events	HR (95% CI)	N	Events	HR (95% CI)
BMI	551	0.151	1.15 (0.96–1.38)	219	0.053	1.10 (0.72–1.68)	135	0.163	1.18 (0.83–1.68)	197	0.262	1.13 (0.87–1.46)
FFM*	432	0.151	1.40 (0.93–2.10)	166	0.054	2.09 (0.77–5.68)	98	0.169	1.52 (0.64–3.62)	152	0.268	1.10 (0.63–1.92)
MNA†	357	0.139	**1.39 (1.18–1.64)**	133	0.060	1.30 (0.77–2.17)	91	0.136	**1.49 (1.10–2.02)**	133	0.227	**1.59 (1.09–1.70)**
Diet quality	357	0.139	**1.22 (1.01–1.48)**	133	0.060	1.15 (0.75–1.77)	91	0.136	1.25 (0.85–1.84)	133	0.227	1.28 (0.99–1.65)
Energy intake	218	0.134	0.86 (0.67–1.10)	96	0.058	1.11 (0.63–1.93)	52	0.151	1.19 (0.69–2.07)	70	0.232	**0.66 (0.48–0.92)**
Protein intake	218	0.134	0.99 (0.78–1.26)	96	0.058	0.64 (0.38–1.09)	52	0.151	0.89 (0.50–1.59)	70	0.232	1.18 (0.85–1.63)
Carbohydrate intake	218	0.134	1.01 (0.79–1.29)	96	0.058	1.20 (0.64–2.28)	52	0.151	1.08 (0.69–1.68)	70	0.232	0.92 (0.65–1.31)
Fat intake	218	0.134	**0.74 (0.59–0.93)**	96	0.058	0.77 (0.44–1.35)	52	0.151	0.86 (0.52–1.42)	70	0.232	**0.67 (0.49–0.92)**
Alcohol intake	218	0.134	**1.34 (1.02–1.76)**	96	0.058	1.47 (0.64–3.40)	52	0.151	1.14 (0.58–2.23)	70	0.232	1.34 (0.97–1.87)

CI, confidence interval; SD, standard deviation.
Data are presented as HR (95% CI), adjusted for age and sex, additionally for baseline diagnosis in the total sample. Events are expressed per person-year. Bold value indicates statistical significant.
*FFM additionally adjusted for body height.
†MNA without item on neuropsychological problems.

Table 3
Adjusted Associations Between Lower Baseline Nutritional Parameters and Clinical Progression; Sensitivity Analyses

Per SD Lower	All			SCD			MCI			AD Dementia		
	N	Events	HR (95% CI)	n	Events	HR (95% CI)	n	Events	HR (95% CI)	n	Events	HR (95% CI)
Amyloid positive patients												
BMI	261	0.212	1.17 (0.91–1.50)	49	0.131	1.14 (0.61–2.11)	64	0.202	1.25 (0.73–2.15)	148	0.248	1.17 (0.84–1.62)
FFM*	204	0.209	1.61 (0.92–2.82)	45	0.121	1.80 (0.51–6.30)	44	0.207	4.46 (0.95–20.93)	115	0.249	1.36 (0.68–2.75)
MNA†	178	0.191	**1.34 (1.07–1.67)**	33	0.137	0.56 (0.15–2.05)	45	0.173	**2.00 (1.20–3.34)**	100	0.218	1.29 (1.00–1.68)
Diet quality	178	0.191	1.24 (0.99–1.55)	33	0.137	1.41 (0.81–2.46)	45	0.173	1.34 (0.84–2.16)	100	0.218	1.24 (0.92–1.67)
Energy intake	104	0.198	0.72 (0.51–1.02)	30	0.123	1.01 (0.49–2.10)	25	0.250	0.81 (0.34–1.92)	49	0.219	**0.59 (0.36–0.96)**
Protein intake	104	0.198	1.03 (0.76–1.41)	30	0.123	0.59 (0.34–1.02)	25	0.250	1.04 (0.52–2.10)	49	0.219	1.44 (0.88–2.36)
Carbohydrate intake	104	0.198	1.23 (0.90–1.68)	30	0.123	1.99 (0.78–5.05)	25	0.250	1.04 (0.56–1.93)	49	0.219	1.19 (0.76–1.84)
Fat intake	104	0.198	**0.64 (0.47–0.86)**	30	0.123	0.66 (0.22–1.96)	25	0.250	0.75 (0.41–1.40)	49	0.219	**0.54 (0.35–0.83)**
Alcohol intake	104	0.198	1.20 (0.85–1.71)	30	0.123	1.08 (0.30–3.84)	25	0.250	1.39 (0.57–3.37)	49	0.219	1.19 (0.79–1.79)
Censoring patients who passed away or were admitted to nursing home												
BMI	551	0.130	1.07 (0.89–1.30)	219	0.045	1.12 (0.71–1.77)	135	0.138	1.16 (0.80–1.69)	197	0.229	1.00 (0.77–1.30)
FFM*	432	0.133	1.15 (0.75–1.76)	181	0.046	1.77 (0.62–5.05)	99	0.144	1.18 (0.48–2.92)	152	0.240	0.90 (0.50–1.62)
MNA†	357	0.122	**1.26 (1.04–1.53)**	133	0.053	1.32 (0.79–2.21)	91	0.126	**1.46 (1.06–2.00)**	133	0.195	1.15 (0.88–1.50)
Diet quality	357	0.122	1.21 (0.99–1.49)	133	0.053	1.09 (0.68–1.74)	91	0.126	1.15 (0.76–1.75)	133	0.195	**1.33 (1.01–1.75)**
Energy intake	218	0.121	0.84 (0.65–1.10)	96	0.053	0.99 (0.55–1.76)	52	0.132	1.36 (0.73–2.54)	70	0.213	**0.66 (0.46–0.93)**
Protein intake	218	0.121	0.98 (0.76–1.26)	96	0.053	0.67 (0.38–1.16)	52	0.132	0.84 (0.46–1.54)	70	0.213	1.16 (0.83–1.62)
Carbohydrate intake	218	0.121	1.06 (0.82–1.37)	96	0.053	1.18 (0.62–2.28)	52	0.132	1.03 (0.64–1.65)	70	0.213	1.05 (0.73–1.50)
Fat intake	218	0.121	**0.72 (0.56–0.91)**	96	0.053	0.79 (0.44–1.42)	52	0.132	0.87 (0.51–1.49)	70	0.213	**0.63 (0.45–0.87)**
Alcohol intake	218	0.121	1.29 (0.98–1.71)	96	0.053	1.40 (0.62–3.17)	52	0.132	1.35 (0.62–2.93)	70	0.213	1.25 (0.90–1.74)
Excluding self- reported progression from the progression definition												
BMI	551	0.084	**1.53 (1.16–2.01)**	219	0.033	1.20 (0.65–2.22)	135	0.113	1.31 (0.85–2.03)	197	0.123	**1.88 (1.22–2.92)**
FFM*	432	0.081	**2.61 (1.47–4.63)**	181	0.035	2.68 (0.71–10.13)	99	0.111	2.15 (0.68–6.75)	152	0.118	**2.63 (1.17–5.92)**
MNA†	357	0.083	**1.47 (1.20–1.80)**	133	0.040	1.08 (0.47–2.51)	91	0.099	**1.48 (1.03–2.11)**	133	0.119	**1.61 (1.23–2.11)**
Diet quality	357	0.083	1.20 (0.94–1.53)	133	0.040	1.34 (0.81–2.23)	91	0.099	1.21 (0.76–1.92)	133	0.119	1.16 (0.82–1.65)
Energy intake	218	0.085	0.91 (0.68–1.23)	96	0.038	1.70 (0.79–3.63)	52	0.123	1.04 (0.59–1.86)	70	0.124	**0.61 (0.40–0.94)**
Protein intake	218	0.085	0.88 (0.65–1.18)	96	0.038	**0.44 (0.26–0.77)**	52	0.123	0.89 (0.48–1.68)	70	0.124	1.28 (0.83–1.97)
Carbohydrate intake	218	0.085	0.96 (0.71–1.31)	96	0.038	2.02 (0.92–4.43)	52	0.123	1.06 (0.65–1.73)	70	0.124	0.61 (0.37–1.03)
Fat intake	218	0.085	0.82 (0.62–1.09)	96	0.038	0.52 (0.24–1.14)	52	0.123	0.93 (0.53–1.64)	70	0.124	0.83 (0.54–1.28)
Alcohol intake	218	0.085	1.43 (0.99–2.08)	96	0.038	1.72 (0.50–5.94)	52	0.123	1.02 (0.51–2.03)	70	0.124	1.54 (0.94–2.53)

CI, confidence interval; SD, standard deviation.
Data are presented as HR (95% confidence interval), adjusted for age and sex additionally for baseline diagnosis in the total sample. Events are expressed per person-year. Bold value indicates statistical significant.
*FFM additionally adjusted for body height;
†MNA without item on neuropsychological problems.

associated with a lower risk of progression [0.74 (0.59–0.93)], whereas a lower alcohol intake was associated with a higher risk of progression [1.34 (1.02–1.76)]. No associations were found for energy, protein, or carbohydrate intake.

After stratification by baseline diagnosis, the effect sizes for BMI and FFM remained comparable for all 3 diagnosis groups (Table 2). Effect sizes for the associations of lower modified MNA score with clinical progression also remained similar and were significant in patients with MCI and AD dementia. For diet quality, effect sizes of the 3 groups were similar to the effect size of the total sample, albeit significance was lost. Analyzing the individual components, poorer adherence to the vegetable guidelines was associated with higher risk of progression in patients with SCD (Supplementary Table 1). In patients with AD dementia, a lower energy and lower fat intake were associated with a lower risk of progression.

When restricting the analyses to patients who were amyloid positive (n = 261), effect sizes remained comparable. Associations for MNA and fat intake remained statistical significant, whereas the associations of diet quality and alcohol intake lost statistical significance (Table 3). Stratified by baseline diagnosis, associations for modified MNA score were mostly attributable to patients with MCI and to lesser extent to patients with AD dementia. Similar to the nonrestricted analyses, a lower energy and fat intake were associated with lower risk of progression in patients with AD dementia.

Subsequently, we performed 2 sensitivity analyses to evaluate the impact of using different definitions of progression. Censoring patients who passed away or were admitted to a nursing home did not change the effect sizes (Table 3). The association of diet quality with progression was comparable in effect size in the total group and stratified for baseline diagnosis. Excluding self-reported progression from the progression definition resulted in larger effect sizes for BMI [1.53 (1.16–2.01)] and FFM [2.61 (1.47–4.63)], other effect sizes remained comparable.

Discussion

The main finding of this study is that poorer nutritional status and less healthy dietary pattern were associated with a higher risk of clinical progression in a memory clinic cohort. Our findings extend on the results of previous studies in cognitively normal adults, by showing that nutritional parameters are determinants of clinical progression in a sample of patients with SCD, MCI, and AD dementia.

In line with and in addition to former studies in patients with moderate AD dementia,[7,8,18–20] we showed that a poorer MNA score, indicative of a poorer nutritional status, was associated with a higher risk of clinical progression across the complete spectrum of AD.[15–17] Furthermore, a lower BMI tended to be associated with a higher risk of clinical progression. In addition, we showed that a lower FFM tended to be associated with a higher risk of clinical progression, with comparable effect sizes as BMI. FFM is rarely assessed in memory clinic patients, although we show that this important indicator of malnutrition[41] provides relevant information in relation to the risk of clinical progression. HRs for MNA, BMI, and FFM were comparable across diagnosis groups, including SCD, indicating that these associations are present for each of these disease stages.

Our finding that a less healthy dietary pattern was associated with a higher risk of clinical progression is in line with former studies in patients with MCI[21] and cognitively normal adults.[10–14,42] In patients with SCD, a lower vegetable intake was associated with higher risk of clinical progression, which is complementary to our previous finding that patients with SCD reporting the lowest vegetable intake had the most cognitive complaints.[43] Previous multidomain lifestyle interventions including dietary advice showed beneficial effects on cognition in individuals at risk of cognitive decline.[44,45] Our study provides further evidence that a healthy dietary pattern is related to a slower rate of clinical progression across the complete AD spectrum, and this could be further evaluated in dietary intervention studies.

Poorer nutritional status is a result of a prolonged disbalance between energy intake and energy expenditure. We did not find an association of energy intake with clinical progression in the total sample, although stratification by baseline diagnosis revealed an association between a lower energy intake and a lower risk of progression in patients with AD dementia. This finding seems paradoxical, although it has been reported that underweight patients with AD dementia have a higher energy intake than patients with a normal weight.[46] We cannot exclude that a higher energy intake in patients with AD dementia might be an active response to previous weight loss to normalize body weight. In line with this notion, we recently found a higher resting energy expenditure in patients with AD dementia compared with controls.[47] Future studies should further examine the potentially higher energy needs of patients with AD dementia.

There is an increasing interest in cardiovascular risk factors and lifestyle as determinants of cognitive decline and dementia.[11] Recent evidence suggests that these factors do not directly influence Alzheimer pathology, but rather exert their beneficial influence through other pathways.[48–50] A crucial question is whether, once the accumulation of AD pathology has started, vascular risk management and lifestyle intervention could still be beneficial to postpone the onset of cognitive decline and dementia. Our results in patients who are amyloid positive showed associations between poorer nutritional status and higher risk of clinical progression remained similar in patients with Alzheimer pathology, providing support for the notion that even when the AD pathologic process has started, lifestyle interventions could still be useful to ameliorate the trajectory of decline.

Among the strengths of this study is the prospective design with the use of different nutritional parameters, including measures of nutritional status and dietary intake. Furthermore, we had a well-characterized and large study population covering patients from the complete AD continuum: cognitively normal (SCD), MCI, and dementia. This study also has some limitations. First, we did not have an annual clinical visit of all patients to assess progression, and defined passing away and nursing home admission as events. Evaluation of whether patients experienced progression of cognitive symptoms was determined asking 1 question; this may not have been reliable. It could be argued that these events might not be classified as clinical progression. Results of our sensitivity analyses, however, showed comparable effect sizes, indicating that the results are not driven by these events. Second, a follow-up time of 2 years is relatively short in the view of a disease process that may take up to 20 years. Especially in patients with SCD 2 years is short, which is also shown by the lower event rates in this group compared with patients with MCI or AD dementia. However, effect sizes were largely comparable across diagnosis groups. Lastly, energy and macronutrient intakes from the FFQ were available for 40% of our sample. Although the group that completed the FFQ was representative for the total sample regarding age, sex, MMSE, and BMI, future studies with data on dietary intake from larger clinical samples are needed to confirm our results. Moreover, we did not have information on physical or social activity or chronic condition, which might confound the relationships.

Conclusions and Implications

In conclusion, in our memory clinic cohort, poorer nutritional status, indicated by a poorer MNA score, lower BMI, and lower FFM, and a less healthy dietary pattern were associated with a higher risk of 2-year clinical progression. The results were largely comparable in patients with SCD, MCI, and AD dementia. This study provides support for investigating whether improving nutritional status can alter the clinical trajectory of AD.

Acknowledgments

We acknowledge members of the NUDAD project team: Amsterdam University Medical Center location VUmc: Wiesje van der Flier, Maartje Kester, Philip Scheltens, Charlotte Teunissen, Marian de van der Schueren, Francien de Leeuw, Astrid Doorduijn, Heleen Hendriksen, Jay Fieldhouse, José Overbeek, Els Dekkers; Vrije Universiteit Amsterdam: Marjolein Visser; Wageningen University and Research: Ondine van de Rest, Sanne Boesveldt; DSM: Peter van-Dael, Manfred Eggersdorfer; Nutricia Research: John Sijben, Nick van Wijk, Amos Attali, J. Martin Verkuyl, Danielle Counotte; FrieslandCampina: Rolf Bos, Cecile Singh-Povel, Martijn Veltkamp, Ellen van den Heuvel.

References

1. Del Parigi A, Panza F, Capurso C, Solfrizzi V. Nutritional factors, cognitive decline, and dementia. Brain Res Bull 2006;69:1–19.
2. Johnson DK, Wilkins CH, Morris JC. Accelerated weight loss may precede diagnosis in Alzheimer disease. Arch Neurol 2006;63:1312–1317.
3. Stewart R, Masaki K, Xue QL, et al. A 32-year prospective study of change in body weight and incident dementia: The Honolulu-Asia aging study. Arch Neurol 2005;62:55–60.
4. Barrett-Connor E, Edelstein SL, Corey-Bloom J, Wiederholt WC. Weight loss precedes dementia in community-dwelling older adults. J Am Geriatr Soc 1996;44:1147–1152.
5. Alhurani RE, Vassilaki M, Aakre JA, et al. Decline in weight and incident mild cognitive impairment: Mayo clinic study of aging. JAMA Neurol 2016;73:439–446.
6. Buchman AS, Wilson RS, Bienias JL, et al. Change in body mass index and risk of incident Alzheimer disease. Neurology 2005;65:892–897.
7. Atti AR, Palmer K, Volpato S, et al. Late-life body mass index and dementia incidence: Nine-year follow-up data from the Kungsholmen Project. J Am Geriatr Soc 2008;56:111–116.
8. Nourhashemi F, Deschamps V, Larrieu S, et al. Body mass index and incidence of dementia: The PAQUID study. Neurology 2003;60:117–119.
9. Roberts RO, Roberts LA, Geda YE, et al. Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. J Alzheimers Dis 2012;32:329–339.
10. Jiang X, Huang J, Song D, et al. Increased consumption of fruit and vegetables is related to a reduced risk of cognitive impairment and dementia: Meta-analysis. Front Aging Neurosci 2017;9:18.
11. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. The Lancet 2017;390:2673–2734.
12. Lourida I, Soni M, Thompson-Coon J, et al. Mediterranean diet, cognitive function, and dementia: A systematic review. Epidemiology 2013;24:479–489.
13. Dominguez LJ, Barbagallo M. Nutritional prevention of cognitive decline and dementia. Acta Biomed 2018;89:276–290.
14. van den Brink AC, Brouwer-Brolsma EM, Berendsen AAM, van de Rest O. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diets are associated with less cognitive decline and a lower risk of Alzheimer's disease: A review. Adv Nutr 2019;10:1040–1065.
15. Vellas B, Lauque S, Gillette-Guyonnet S, et al. Impact of nutritional status on the evolution of Alzheimer's disease and on response to acetylcholinesterase inhibitor treatment. J Nutr Health Aging 2005;2:75–80.
16. Ousset PJ, Nourhashemi F, Reynish E, Vellas B. Nutritional status is associated with disease progression in very mild Alzheimer disease. Alzheimer Dis Assoc Disord 2008;22:66–71.
17. Guerin O, Soto M, Brocker P, et al. Nutritional status assessment during Alzheimer's disease: Results after one year (the REAL French study group). J Nutri Health Aging 2005;9:81–84.
18. Besser LM, Gill DP, Monsell SE, et al. Body mass index, weight change, and clinical progression in mild cognitive impairment and Alzheimer disease. Alzheimer Dis Assoc Disord 2014;28:36–43.
19. Cronk BB, Johnson DK, Burns JM. the Alzheimer's Disease Neuroimaging Initiative. Body mass index and cognitive decline in mild cognitive impairment. Alzheimer Dis Assoc Disord 2010;24:126–130.
20. Sobow T, Fendler W, Magierski R. Body mass index and mild cognitive impairment-to-dementia progression in 24 months: A prospective study. Eur J Clin Nutr 2014;68:1216–1219.
21. Singh B, Parsaik AK, Mielke MM, et al. Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis. J Alzheimers Dis 2014;39:271–282.
22. Folstein M, Folstein S, McHugh P. "Mini-mental state" a practical method for grading the cognitive state of patients for the clinician. J Psychiat Res 1975;12:189–198.
23. Doorduijn AS, Visser M, van de Rest O, et al. Associations of AD biomarkers and cognitive performance with nutritional status: The NUDAD project. Nutrients 2019;1:1161.
24. van der Flier WM, Scheltens P. Amsterdam Dementia Cohort: Performing research to optimize care. J Alzheimers Dis 2018;62:1091–1111.
25. van der Flier WM, Pijnenburg YA, Prins N, et al. Optimizing patient care and research: The Amsterdam Dementia Cohort. J Alzheimers Dis 2014;41:313–327.
26. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–269.
27. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–279.
28. Vellas B, Villars H, Abellani G, et al. Overview of the MNA: Its history and challenges. J Nutri Health Aging 2006;10:456–465.
29. Guigoz Y. The Mini-Nutritional Assessment (MNA) review of the literature–What does it tell us? J Nutr Health Aging 2006;10:466–485.
30. van Lee L, Geelen A, van Huysduynen EJH, et al. The Dutch Healthy Diet index (DHD-index): An instrument to measure adherence to the Dutch Guidelines for a Healthy Diet. Nutrition J 2012;11:49.
31. Guidelines for a healthy diet 2006. The Hague: Health Council of the Netherlands; 2006. publication no. 2006/21E.
32. Beukers MH, Dekker LH, de Boer EJ, et al. Development of the HELIUS food frequency questionnaires: Ethnic-specific questionnaires to assess the diet of a multiethnic population in the Netherlands. Eur J Clin Nutr 2015;69:579–584.
33. RIVM. Dutch Food composition table (NEVO-table 2013). Bilthoven, the Netherlands; 2013.
34. de Wilde A, van Maurik IS, Kunneman M, et al. Alzheimer's biomarkers in daily practice (ABIDE) project: Rationale and design. Alzheimers Dement (Amst) 2017;6:143–151.
35. Teunissen C, Petzhold A, Bennett J, et al. A consensus protocol for the standardization of cerebrospinal fluid collection and biobanking. Neurology 2009;73:1914–1922.
36. Mulder C, Verwey NA, van der Flier WM, et al. Amyloid-beta (1-42), total tau, and phosphorylated tau as cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease. Clin Chem 2010;56:248–253.
37. Tijms BM, Willemse EAJ, Zwan MD, et al. Unbiased approach to counteract upward drift in cerebrospinal fluid amyloid-beta 1-42 analysis results. Clin Chem 2018;64:576–585.
38. Heiat A, Vaccarino V, Krumholz HM. An evidence-based assessment of federal guidelines for overweight and obesity as they apply to elderly persons. Arch Intern Med 2001;161:1194–1203.
39. Di Angelantonio E, Bhupathiraju SN, Wormser D, et al. Body-mass index and all-cause mortality: Individual-participant-data meta-analysis of 239 prospective studies in four continents. The Lancet 2016;388:776–786.
40. Schutz Y, Kyle UG, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y. Int J Obes 2002;26:953–960.
41. Jensen GL, Cederholm T, Correia M, et al. GLIM Criteria for the diagnosis of malnutrition: A consensus report from the global clinical nutrition community. JPEN J Parenter Enteral Nutr 2019;43:32–40.
42. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. Alzheimers Dement 2015;11:1015–1022.
43. Wesselman LMP, Doorduijn AS, de Leeuw FA, et al. Dietary patterns are related to clinical characteristics in memory clinic patients with subjective cognitive decline: The SCIENCe project. Nutrients 2019;11:5.
44. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. Lancet 2015;385:2255–2263.
45. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. Lancet Neurol 2017;16:377–389.
46. Wang PN, Yang CL, Lin KN, et al. Weight loss, nutritional status and physical activity in patients with Alzheimer's disease. A controlled study. J Neurol 2004;25:314–320.
47. Doorduijn AS, de van der Schueren MAE, van de Rest O, et al. Energy intake and expenditure in patients with Alzheimer's disease and mild cognitive impairment: The NUDAD project. Alzheimer Res Ther 2020;12:116.
48. Lane CA, Barnes J, Nicholas JM, et al. Associations between vascular risk across adulthood and brain pathology in late life: Evidence from a British birth cohort. JAMA Neurol 2020;77:175–183.
49. Gottesman RF, Mosley TH, Knopman DS, et al. Association of intracranial atherosclerotic disease with brain beta-amyloid deposition: Secondary analysis of the ARIC Study. JAMA Neurol 2020;77:350–357.
50. Gustavsson AM, van Westen D, Stomrud E, et al. Midlife atherosclerosis and development of Alzheimer or vascular dementia. Ann Neurol 2020;87:52–62.

Appendix

Supplementary Table 1
Adjusted Associations Between Lower Adherence of Diet Quality Components and Progression in the Total Sample and Stratified for Baseline Diagnosis

Per SD Lower	All			SCD			MCI			AD Dementia		
	N	Events	HR (95% CI)	n	Events	HR (95% CI)	n	Events	HR (95% CI)	n	Events	HR (95% CI)
Vegetables	357	0.139	1.17 (0.95–1.43)	133	0.060	**1.57 (1.02–2.42)**	91	0.136	1.22 (0.77–1.92)	133	0.227	1.07 (0.80–1.42)
Fruit	357	0.139	1.17 (0.98–1.41)	133	0.060	1.00 (0.60–1.67)	91	0.136	1.19 (0.83–1.70)	133	0.227	1.22 (0.96–1.54)
Fibers	357	0.139	1.03 (0.85–1.25)	133	0.060	1.21 (0.77–1.88)	91	0.136	0.84 (0.55–1.26)	133	0.227	1.04 (0.80–1.35)
Fish	357	0.139	1.07 (0.88–1.31)	133	0.060	0.93 (0.59–1.46)	91	0.136	0.93 (0.63–1.38)	133	0.227	1.24 (0.94–1.65)
Saturated fat	357	0.139	1.06 (0.87–1.29)	133	0.060	0.82 (0.50–1.33)	91	0.136	1.28 (0.88–1.88)	133	0.227	1.10 (0.84–1.42)
Trans fat	357	0.139	1.09 (0.90–1.32)	133	0.060	1.01 (0.63–1.61)	91	0.136	1.10 (0.74–1.63)	133	0.227	1.16 (0.90–1.49)
Salt	357	0.139	1.17 (0.97–1.42)	133	0.060	1.18 (0.73–1.91)	91	0.136	1.44 (1.00–2.08)	133	0.227	1.06 (0.81–1.38)
Alcohol	357	0.139	1.02 (0.85–1.22)	133	0.060	1.23 (0.82–1.93)	91	0.136	0.71 (0.41–1.24)	133	0.227	1.06 (0.85–1.31)

CI, confidence interval; SD, standard deviation.
Data are presented as HR (95% CI), adjusted for age and sex, additionally for baseline diagnosis in the total sample. Events are expressed per person-year. Bold value indicates statistical significant.