

Original Research Article

# Association of Adherence to a Healthy Diet with Cognitive Decline in European and American Older Adults: A Meta-Analysis within the CHANCES Consortium

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## Keywords

Ageing · Diet · Nutrition · CHANCES · Cognition · Cohort · Epidemiology · Healthy Diet Indicator

## Abstract

**Aim:** To examine the association between a healthy diet, assessed by the Healthy Diet Indicator (HDI), and cognitive decline in older adults. **Methods:** Data from 21,837 participants aged ≥55 years from 3 cohorts (Survey in Europe on Nutrition and the Elderly, a Concerted Action

[SENECA], Rotterdam Study [RS], Nurses' Health Study [NHS]) were analyzed. HDI scores were based on intakes of saturated fatty acids, polyunsaturated fatty acids, mono- and disaccharides, protein, cholesterol, fruits and vegetables, and fiber. The Telephone Interview for Cognitive Status in NHS and Mini-Mental State Examination in RS and SENECA were used to assess cognitive function from multiple repeated measures. Using multivariable-adjusted, mixed linear regression, mean differences in annual rates of cognitive decline by HDI quintiles were estimated. **Results:** Multivariable-adjusted differences in rates in the highest versus the lowest HDI quintile were 0.01 (95% CI –0.01, 0.02) in NHS, 0.00 (95% CI –0.02, 0.01) in RS, and 0.00 (95% CI –0.05, 0.05) in SENECA with a pooled estimate of 0.00 (95% CI –0.01, 0.01),  $I^2 = 0\%$ . **Conclusions:** A higher HDI score was not related to reduced rates of cognitive decline in European and American older adults.

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## Introduction

The world's population aged over 60 years is predicted to double from 11 to 22% between 2000 and 2050 [1]. This demographic shift is likely to further increase the prevalence of age-related diseases and disabilities in the near future. In 2013, there were 44.4 million people with dementia worldwide, and this number will increase to an estimated 135.5 million in 2050 [2]. Identifying modifiable risk factors for cognitive decline as a precursor of dementia is likely to be an important strategy for delaying the onset, and reducing the number of people with dementia [3]; a healthy diet is hypothesized to reduce risk [4].

A common approach to explore the impact of nutrition is studying dietary patterns comprising combinations of nutrients and foods. A frequently studied dietary pattern is the Mediterranean diet, which is rich in fruits and vegetables and unsaturated fatty acids. Greater adherence to the Mediterranean diet has been associated with a lower rate of cognitive decline in a number of observational and interventional studies [5]. However, there is a need to jointly study information from multiple studies to establish clear associations between a healthful dietary pattern, cognitive function, and cognitive decline.

Recommending dietary patterns at an international level requires the operationalization of globally applicable dietary guidelines. Therefore, the 1990 World Health Organization (WHO) guidelines for a healthy diet [6] were translated into the Healthy Diet Indicator (HDI) [7, 8]. These guidelines were developed to reduce chronic diseases, such as hypertension. As hypertension has been shown to impact cognitive function [9–11], it has been hypothesized that the HDI could reduce cognitive function decline.

The HDI based on initial WHO recommendations has been associated with a lower prevalence of cognitive impairment [12, 13]; however, the association between updated WHO guidelines and cognitive decline has not been quantified. We therefore prospectively examined the association between baseline HDI and cognitive decline at older age among 21,837 men and women from Europe and the US by conducting a meta-analysis of individual participant data from 3 population-based cohorts involved in the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) [14]. We hypothesized that a higher HDI score would be related to less cognitive decline.

## Materials and Methods

### *Data Assessment and Harmonization*

The aim of CHANCES is to combine prospective cohort studies to produce, improve, and clarify the evidence on the distribution and risk factors of chronic diseases in the elderly and on their socioeconomic impact ([www.chancesfp7.eu](http://www.chancesfp7.eu)). Data standardization and harmonization procedures were largely based upon

the experience from the MORGAM project and previous experiences of project partners [15]. Data assessment procedures included examination of availability and comparability of cohort data, questionnaires and measurement procedures used in the individual cohorts, and methods for collection of data on health outcomes [14, 16]. For the present study, CHANCES cohorts were selected with harmonized variables on dietary intake and cognitive function, and covariates according to predefined rules.

#### *Study Design and Population*

We included participants aged  $\geq 55$  years from 3 cohorts, namely the cognitive substudy of the Nurses' Health Study (NHS) from the US [17]; the Rotterdam Study (RS) from the Netherlands [18]; and the Survey in Europe on Nutrition and the Elderly, a Concerted Action (SENECA) Study from Europe (Belgium, Denmark, France, Italy, The Netherlands, Portugal, Spain, Switzerland, and Poland) [19].

NHS began in 1976, with 121,700 female registered nurses aged 30–55 years [17]. During 1995–2001, women aged  $\geq 70$  years were invited to participate in a telephone-based study of cognitive function. For the first interview, 93% of eligible women participated ( $n = 19,415$ ). Follow-up assessments were performed up to 3 times at 2-year intervals. RS began baseline measures between 1990 and 1993 in 7,983 men and women aged  $\geq 55$  years [20]. The first follow-up examination took place between 1993 and 1994 in 6,315 participants (follow-up 88%) and continued in 1997, 1999, and 2001. The total SENECA population consisted of 2,585 European men and women aged 70–75 years at inclusion in 1988, and 124 participants were additionally added in a second wave in 1993. Follow-up measures were performed in 1993 and 1998 [19]. In all cohorts, the collaborative research procedures were in accordance with the ethical standards of the responsible institutional or regional committees on human experimentation and informed consent was obtained from all participants.

#### *Dietary Assessment*

Information on dietary intake was obtained with a validated 116-item semiquantitative Food Frequency Questionnaire (FFQ) in NHS in 1994 and 1998 [17] and a validated 170-item FFQ in RS at baseline (1990–1993) [20]. In SENECA, dietary intake was assessed in 1988 ( $n = 2,585$ ) and 1993 ( $n = 1,301$ ) by means of a dietary history method including a 3-day food record and a frequency checklist of foods [19]. Participants were interviewed by a dietician about their usual food consumption per day during the past month. Food intake estimations were converted into nutrient intakes by multiplying the consumption of each food by its nutrient content, using the US Department of Agriculture database in NHS and the Dutch food composition table (NEVO) [21] in RS and SENECA. The FFQs and dietary history method provided information allowing to estimate usual dietary intake per day during a specified period of time.

#### *Healthy Diet Indicator*

We used dietary intake immediately preceding the first cognitive assessment (ranging from 0 to 3 years across the 3 cohorts) to estimate daily energy intake and to assess adherence to the updated WHO dietary guidelines in 2003 [8]. From 15 dietary items listed in the guidelines, 7 items from which information was available across all cohorts were included in the HDI. This resulted in an HDI including saturated fatty acids, polyunsaturated fatty acids (PUFAs), mono- and disaccharides, protein, cholesterol, fruits and vegetables, and dietary fiber. Not included in the score were the intake of n-3 PUFAs, n-6 PUFAs, trans-fatty acids, and sodium due to unavailability of data across cohorts. Furthermore, as suggested before [7], we excluded total fat and total carbohydrates from the HDI score calculation to avoid duplicating weights for these 2 components by the component factors and excluded nonstarch polysaccharide as it also overlapped with the recommendation for total dietary fiber. We also excluded monounsaturated fatty acids (MUFAs), because the WHO guideline does not clearly specify the recommended intake of MUFAs in contrast to other fats. We applied a recently developed continuous HDI scoring system [22] with scores ranging from 0 to 10 per dietary component to provide greater variation between individuals and to overcome the use of definite cutoffs [22]. Intakes below the lower cutoff were assigned 0 points and intakes above the upper cutoff were assigned 10 points. Within a given range of intakes for each component, the range was divided into 10, and points were given in proportion to the distance from the 0 point cutoff. The scoring criteria, as well as the median component scores by cohort are shown in Table 1. Total HDI scores were divided into sex- and cohort-specific quintiles based on study population intake distributions.

**Table 1.** Scoring criteria of the HDI components based on the WHO's 2003 guidelines for a healthy diet and mean component intakes by country and sex

HDI component <sup>a</sup>	0 points	0–10 points <sup>e</sup>	10 points	NHS (women)	RS		SENECA	
					men	women	men	women
Saturated fatty acids, en% <sup>b,c</sup>	>15	≥10–≤15	0–<10	9.3 (2.8)	14.9 (3.1)	14.7 (3.3)	14.3 (4.4)	14.8 (4.4)
Mono- and disaccharides, en% <sup>b,d</sup>	>30	≥10–≤30	0–<10	27.3 (7.3)	21.6 (6.2)	22.7 (5.9)	19.1 (6.5)	20.3 (7.1)
Cholesterol, mg/day <sup>c</sup>	>400	≥300–≤400	0–<300	181.5 (88.4)	259.1 (88.8)	215.5 (69.2)	314.9 (132.2)	272.0 (121.9)
Polyunsaturated fatty acids, en% <sup>b,c</sup>	>10	0–<6	≥6–≤10	5.6 (1.8)	7.6 (2.9)	6.9 (2.8)	6.2 (3.9)	6.2 (3.2)
Protein, en% <sup>b</sup>	>20	0–<10 or >15–≤20	≥10–≤15	17.0 (3.2)	17.0 (2.9)	17.9 (3.2)	15.1 (2.7)	15.1 (3.2)
Total dietary fiber, g/day	0	0–<25	≥25	5.4 (2.2)	18.3 (5.3)	16.2 (4.5)	22.2 (7.7)	18.5 (6.6)
Fruits and vegetables, g/day	0	0–<400	≥400	400.8 (206.6)	429.0 (170.3)	461.8 (180.1)	563.3 (257.5)	497.3 (213.5)

HDI, Healthy Diet Indicator; WHO, World Health Organization; NHS, Nurses' Health Study; RS, Rotterdam Study; en%, energy percent. Values are mean (SD).  
<sup>a</sup> Standard in accordance with WHO guidelines. The joint WHO Food and Agriculture Organization of the United Nations guidelines of 2003 do not clearly indicate fiber cutoff values. Fulfillment of the fruit and vegetable recommendation and consumption of whole grains should sum to 20 g of nonstarch polysaccharides, which equals approximately 25 g of dietary fiber. Total fat and total carbohydrates were excluded to avoid overlap with other components of the score. <sup>b</sup> Calculated without energy from alcohol. <sup>c</sup> The cutoff value at which a participant would score 0 points was based on the 85th percentile of the population's intake distribution. Calculation of points for dietary intake between the upper limit and the standard intake for maximum number of points: 10 – (intake – recommendation upper limit) × (10/standard upper limit – recommendation upper limit). <sup>d</sup> Mono- and disaccharides were studied instead of free sugars. <sup>e</sup> The range was divided into 10 and then points were given in proportion to the distance from the 0 point cutoff.

### Assessment of Cognitive Function

In NHS, the Telephone Interview of Cognitive Status (TICS) [23], a telephone adaptation of the Mini-Mental State Examination (MMSE) was administered first at baseline (1995–2001), then at approximately 2-year intervals, with up to 3 repeated measures. The TICS contains measures of orientation, immediate verbal recall, registration, opposites, current events, serial subtraction, counting, and other elements and assesses global cognitive performance, with scores ranging from 0 to 41.

The MMSE [24] assessed global cognitive function in RS in 1990, 1993, 1997, 1999, and 2001, and in SENECA in 1993 and 1999. The MMSE includes questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction, resulting in a score from 0 to 30. A correlation of 0.94 between TICS and MMSE and a high test-retest reliability for TICS ( $r = 0.97$ ) was reported [23]. Higher TICS or MMSE scores indicate better cognitive performance.

We calculated z-scores at each time point using cohort-specific distributions of scores at first cognitive assessment allowing comparability of findings across cohorts.

### Other Variables

Demographic, health, and lifestyle information was obtained from self-administered questionnaires. Height and weight were measured at baseline in RS and SENECA and self-reported in NHS [25]. Physical activity was assessed by validated questionnaires for elderly by estimating mean energy expended per week in NHS (in metabolic equivalent-hours, METs) and as being vigorously physically active in SENECA and RS. In RS, physical activity was assessed 6 years after baseline as no baseline measure was available. Prevalence of diabetes mellitus, myocardial infarction, high blood pressure, depression, and hypercholesterolemia was obtained by questionnaires. In SENECA, hypercholesterolemia was estimated on use of dyslipidemia medications.

### Population for Analysis

We excluded participants with incomplete dietary intake data ( $n = 2,144$  NHS,  $n = 2$  RS,  $n = 16$  SENECA), without at least 1 cognitive assessment ( $n = 1,771$  RS,  $n = 1,676$  SENECA), and missing data for physical activity ( $n = 111$  NHS,  $n = 1,769$  RS), resulting in a total population of 21,837 participants (17,160 NHS, 3,660 RS, and 1,017 SENECA).

### Statistical Analyses

Means and standard deviations were calculated for normally distributed continuous variables, and numbers and percentages were calculated for categorical variables.

In the primary approach, we modelled trajectories of repeated cognitive measures using linear mixed models [26], with follow-up time from baseline as the time metameter. The linear model included an intercept representing the baseline level of cognitive score and a slope representing annual cognitive change as well

as a random intercept and random slope accounting for interindividual variability. Linear trends across quintiles of HDI score were examined using a continuous variable in which participants in a given HDI quintile were assigned the median value.

In a secondary approach, all repeated measures of cognitive function were averaged to create an outcome representing long-term cognitive status. Averaging repeated measures of cognition attenuates variability in each single cognitive assessment, which may be helpful when cognition is measured over a relatively short follow-up period with a modest decline over time in healthy, educated participants in NHS, RS, and SENECA [17, 27]. Mean differences in cognitive status across quintiles of HDI score were modelled using linear regression.

Adjustments were made for confounding factors that have been related to both dietary intake and cognitive function: age, sex, education (low, middle, high) (model 1), and employment history (employed, housekeeper, unemployed/retired), BMI (<22, 22–25, ≥25–30, ≥30 kg/m<sup>2</sup>), smoking status (never, former, current), energy intake (cohort specific quintiles), alcohol intake (<1, 1–14.9, ≥15 g/day), physical activity (yes/no vigorous exercise in RS and SENECA, quintiles of METS in NHS), and depression (yes/no) (model 2). Vascular conditions (history of diabetes [yes/no], myocardial infarction [yes/no], high blood pressure [yes/no], and hypercholesterolemia [yes/no]) were tested as mediators by adding them to the full model (model 3). In the linear regression model studying long-term cognitive status, a study center variable was added to SENECA to adjust for differences in baseline MMSE score between study centers. For BMI, 4.4% was missing in NHS; for employment, data were missing for 3.7% in RS; in SENECA, data were missing for education (5.9%) and depression (15%); thus, a specific missing category was created for these 4 variables. For all other covariates, participants with missing information were <1% of the sample and were assigned to the reference group. In subgroup analyses, we repeated our primary analyses while stratifying by sex (not applicable in NHS), baseline cognitive function (worst 10% vs. best 90%), age (median split), BMI (<25 vs. ≥25), and having any major cardiovascular risk factor (high blood pressure, hypercholesterolemia, myocardial infarction). As a sensitivity analysis, we determined the potential impact on our estimates of a learning effect when participants are administered the same cognitive tests multiple times by averaging the first 2 cognitive assessments within NHS and RS to derive a more robust baseline measure variable as first cognitive assessment and then repeating our analysis.

Subsequently, we summarized the multivariable-adjusted mean differences in slopes of the fifth quintile versus first quintile per cohort by random effects pooling by using DerSimonian and Laird random effects models [28], accounting for differences in sample size and the possibility of statistical heterogeneity among the studies. Between-study heterogeneity was assessed using the *I*<sup>2</sup> statistic [29], expressing the percentage of variation attributable to between-study heterogeneity. All statistical analyses were carried out using SAS, version 9.3, software (SAS Institute Inc., Cary, NC, USA). For random effects meta-analyses, we used the *metaphor* package in R, version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). *p* values <0.05 were considered significant.

## Results

### *General Characteristics*

Median HDI scores were 44.6 (range 13.3–62.5) in NHS, 45.5 (range 14.4–62.9) in RS, and 47.9 (range 20.6–69.9) in SENECA. At the first cognitive assessment, mean age of participants was 74.2 (2.3) years in NHS, 65.7 (7.3) in RS, and 78.0 (2.8) in SENECA. Across all cohorts, participants with a higher HDI score were more likely to be physically active, higher educated, never smokers, normal weight, to have higher energy intakes, and a history of myocardial infarction and to be less likely to have a history of diabetes (Table 2).

### *Relation between HDI Score and Cognitive Decline*

A higher HDI score was not associated with cognitive decline in the basic adjusted model (adjusted mean differences in rates between extreme quintiles = 0.005 [95% CI –0.005, 0.016], *p* trend = 0.17 in NHS, 0.001 [95% CI –0.014, 0.015], *p* trend = 0.69 in RS, and 0.008 [95% CI –0.041, 0.052], *p* trend = 0.49 in SENECA), or in the multivariable-adjusted model (0.005, [95% CI –0.006, 0.016]), *p* trend = 0.20 in NHS, –0.002 [95% CI –0.016, 0.013], *p* trend = 0.98 in RS



**Table 2.** Baseline characteristics of participants in the NHS ( $n = 17,160$ ), RS ( $n = 3,660$ ) and SENECA ( $n = 1,017$ ) by extreme cohort- and sex-specific quintiles of HDI score

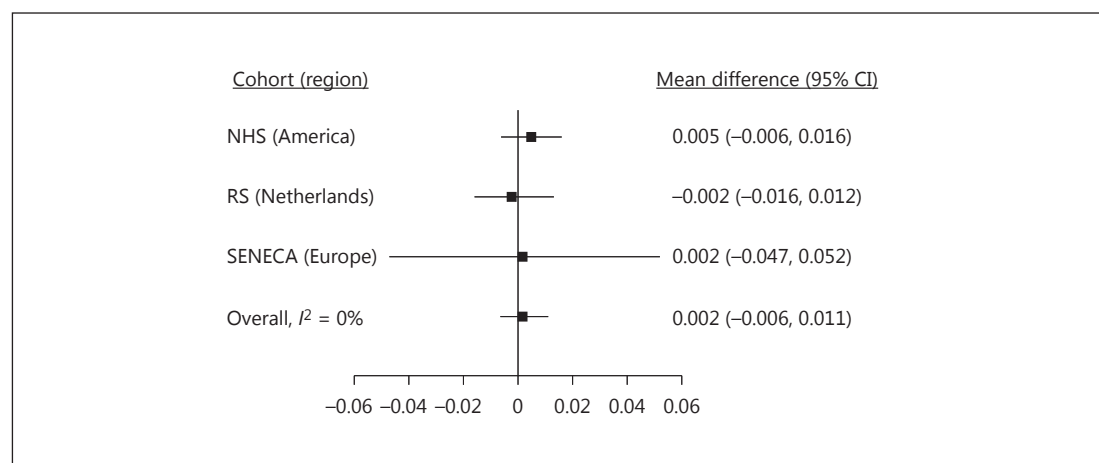
	NHS		RS		SENECA	
	quintile 1 ( $n = 3,422$ )	quintile 5 ( $n = 3,431$ )	quintile 1 ( $n = 731$ )	quintile 5 ( $n = 731$ )	quintile 1 ( $n = 202$ )	quintile 5 ( $n = 203$ )
HDI score	35.7 [32.6–37.7]	52.7 [51.4–54.4]	36.4 [33.8–38.2]	53.2 [51.9–55.2]	38.1 [35.4–40.2]	57.1 [55.3–59.23]
Age, years	74.1 (2.3)	74.4 (2.4)	66.3 (7.4)	65.6 (6.3)	77.8 (2.8)	78.0 (2.8)
Men	N/A	N/A	40.8	40.8	49.0	48.8
Educational level						
Low	78	77	34	29	53	49
Middle	16	16	57	60	30	33
High	6	6	8	11	10	10
BMI						
$\leq 21$	19	22	8	11	9	12
22–24	24	27	28	34	22	20
25–29	33	34	50	44	43	44
$\geq 30$	20	14	15	12	20	14
Physical activity <sup>a</sup>	13.8 (18.7)	18.3 (22.1)	83	89	8	9
Employment history						
Employed	5	4	79	78	75	78
Homemaker	7	7	11	9	17	12
Other/retired	88	89	10	13	9	10
Smoking						
Never	44	48	30	36	55	60
Former	44	46	39	46	30	30
Current	12	6	31	18	15	10
History of disease						
Myocardial infarction	6	5	9	11	24	32
Hypertension	56	55	36	37	32	37
Hypercholesterolemia	60	67	2	3	11	6
Diabetes	11	9	9	6	16	13
Depression	10	9	9	9	19	19
Dietary variables						
Energy intake, kcal	1,518 (572)	1,806 (497)	2,007 (609)	2,053 (414)	1,897 (618)	2,071 (607)
Alcohol, g	5.3 (10.4)	4.6 (8.6)	12.1 (15.8)	7.46 (10.6)	12.6 (18.1)	10.7 (8.9)
HDI components						
Saturated fatty acids	11.7 (3.2)	8.1 (1.7)	16.9 (3.1)	13.1 (2.5)	16.6 (4.4)	12.2 (3.6)
PUFAs	5.5 (2.3)	6.3 (1.4)	6.5 (3.6)	7.7 (1.7)	6.3 (4.1)	6.4 (2.2)
Mono- and disaccharides	26.2 (7.8)	26.2 (6.1)	21.5 (6.1)	23.2 (6.0)	20.8 (7.3)	17.9 (6.3)
Protein	18.5 (3.5)	15.0 (1.9)	18.6 (3.3)	16.2 (2.4)	16.9 (3.9)	13.9 (1.7)
Cholesterol, g	221 (121)	166 (68)	285 (105)	204 (55)	351 (144)	239 (78.5)
Fruit and vegetables, g	286 (172)	505 (205)	395 (193)	500 (149)	465 (246)	604 (255)
Dietary fiber, g	4.1 (1.9)	6.8 (2.3)	14.6 (4.7)	20.1 (4.4)	17.0 (6.9)	23.9 (7.5)
MMSE/TICS	33.8 (2.7)	33.8 (2.7)	27.9 (1.5)	28.1 (1.6)	26.9 (2.7)	26.3 (2.7)

HDI, Healthy Diet Indicator; NHS, Nurses' Health Study; RS, Rotterdam Study; PUFAs, polyunsaturated fatty acids. Data are presented as median [IQR], mean (SD), or %. <sup>a</sup> Physical activity in NHS represented in metabolic-equivalent hours, in RS and SENECA as % vigorous physical activity. Dietary variables represent mean intakes per day expressed in energy percentages, unless otherwise noted.

**Table 3.** Multivariable-adjusted mean differences in annual rates of cognitive change by cohort- and sex-specific quintiles of baseline HDI score

	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>
<i>NHS (n = 17,160)</i>		
Quintile 1	Ref.	Ref.
Quintile 2	-0.004 (-0.014, 0.006)	-0.004 (-0.014, 0.007)
Quintile 3	0.013 (0.003, 0.023)	0.012 (0.002, 0.023)
Quintile 4	0.002 (-0.008, 0.012)	0.002 (-0.009, 0.012)
Quintile 5	0.005 (-0.005, 0.016)	0.005 (-0.006, 0.016)
<i>p</i> trend	0.17	0.20
<i>RS (n = 3,660)</i>		
Quintile 1	Ref.	Ref.
Quintile 2	0.000 (-0.014, 0.015)	0.000 (-0.015, 0.014)
Quintile 3	0.012 (-0.003, 0.026)	0.010 (-0.004, 0.025)
Quintile 4	0.004 (-0.011, 0.018)	0.002 (-0.013, 0.016)
Quintile 5	0.001 (-0.014, 0.015)	-0.002 (-0.016, 0.013)
<i>p</i> trend	0.69	0.98
<i>SENECA (n = 1,017)</i>		
Quintile 1	Ref.	Ref.
Quintile 2	-0.015 (-0.063, 0.034)	-0.029 (-0.079, 0.019)
Quintile 3	0.022 (-0.028, 0.071)	0.017 (-0.033, 0.066)
Quintile 4	0.006 (-0.043, 0.055)	0.000 (-0.049, 0.049)
Quintile 5	0.008 (-0.041, 0.057)	0.002 (-0.047, 0.052)
<i>p</i> trend	0.49	0.52

HDI, Healthy Diet Indicator; NHS, Nurses' Health Study; RS, Rotterdam Study; Ref., reference. Values are mean differences (95% confidence interval). <sup>a</sup>Adjusted for age, gender, and education. <sup>b</sup>Additionally adjusted for employment status, BMI, smoking status, energy intake, alcohol intake, physical activity, and depression.



**Fig. 1.** Cohort- and sex-specific and pooled mean differences in the annual rate of cognitive change in relation to highest vs. lowest quintile of adherence to the WHO guidelines and cognitive decline, adjusted for age, gender (TS and SENECA), education, employment status, BMI, smoking status, calorie intake, alcohol intake, physical activity, and depression in the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES), 1988–2011. Cohorts are ordered according to cohort size, beginning with the largest cohort.  $I^2$  is expressed as the percentage of total variability caused by heterogeneity. All data were obtained from CHANCES (www.chancesfp7.eu). Bars indicate 95% confidence intervals (CIs). NHS, Nurses' Health Study; RS, Rotterdam Study; SENECA, Survey in Europe on Nutrition and the Elderly, a Concerted Action.

**Table 4.** Multivariable-adjusted mean differences in annual rates of cognitive change by cohort- and sex-specific quintiles of baseline HDI score by cardiovascular risk factor history in SENECA

	No cardiovascular risk factor (n = 495)	Cardiovascular risk factor (n = 522)
Quintile 1	Ref.	Ref.
Quintile 2	-0.077 (-0.149, -0.005)	0.022 (-0.045, 0.087)
Quintile 3	-0.053 (-0.128, 0.021)	0.076 (0.010, 0.142)
Quintile 4	-0.061 (-0.132, 0.010)	0.076 (0.009, 0.143)
Quintile 5	-0.048 (-0.122, 0.027)	0.056 (-0.009, 0.121)
p trend	0.23	0.03
p interaction		0.03

HDI, Healthy Diet Indicator; Ref., reference. Cardiovascular risk factor or disease included high blood pressure, hypercholesterolemia, or myocardial infarction. Values are mean differences (95% confidence interval). Scores were adjusted for age, education, study center, employment status, BMI, smoking status, energy intake, alcohol intake, physical activity, and depression.

and 0.002 [95% CI -0.047, 0.052], *p* trend = 0.52 in SENECA) (Table 3). Pooled analyses showed no association between highest HDI scores and cognitive decline (pooled multivariable-adjusted mean difference = 0.002 [95% CI: -0.006, 0.011], *I*<sup>2</sup> = 0%) (Fig. 1). Adding mediators to the model (type 2 diabetes mellitus, myocardial infarction, hypertension, and hypercholesterolemia) did not affect the estimates (adjusted mean differences in rates between extreme quintiles 0.006 [95% CI -0.005, 0.017], *p* trend = 0.15 in NHS, -0.002 [95% CI -0.017, 0.012], *p* trend = 0.98 in RS, and -0.001 [95% CI -0.049, 0.048], *p* trend = 0.56 in SENECA, respectively). Subgroup analyses by sex, baseline cognitive function, age, and BMI did not show differences by strata or statistical interaction. Among those with a history of cardiovascular risk factors, there was less cognitive decline with the highest HDI score in SENECA (*p* trend = 0.03, *p* interaction = 0.03; Table 4). Furthermore, in sensitivity analyses to address practice effects, in the RS and NHS where >2 repeated measures were available, we used models where the average of the first 2 cognitive assessments was considered as the new baseline from which cognitive change was evaluated; the results did not differ from the main analyses (data not shown).

#### *Relation between the HDI Score and Cognitive Status*

The HDI score was not associated with cognitive status in NHS, RS, and SENECA in the basic adjusted model (*p* trend = 0.28 in NHS, 0.19 in RS, and 0.34 in SENECA), or in the multivariable-adjusted model (*p* trend = 0.87 in NHS, 0.27 in RS, and 0.25 in SENECA) (Table 5).

## **Discussion**

In the present consortium study, including 21,837 older men and women from Europe and the US, we found that a healthier diet adhering to the most recent WHO guidelines was not associated with a slower rate of cognitive decline, nor with cognitive status at older ages, which is in contrast to the findings between other dietary patterns [30–32] and cognition.

As the HDI was developed to prevent chronic diseases, we hypothesized that it could also impact cognitive function. Previously, 2 cross-sectional studies assessed the association between a higher HDI score and cognitive impairment and reported a lower prevalence of cognitive impairment in 1,049 Italian older men (odds ratio 0.75 [95% CI 0.58–0.97] [13])



**Table 5.** Multivariable-adjusted mean differences in average cognitive status by cohort- and sex-specific quintiles of baseline HDI score

	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>
<i>NHS (n = 16,807)</i>		
Quintile 1	Ref.	Ref.
Quintile 2	0.00 (–0.04, 0.05)	–0.02 (–0.06, 0.03)
Quintile 3	0.04 (–0.01, 0.08)	0.01 (–0.03, 0.06)
Quintile 4	0.00 (–0.04, 0.05)	–0.02 (–0.07, 0.02)
Quintile 5	0.03 (–0.02, 0.07)	0.00 (–0.04, 0.04)
<i>p</i> trend	0.28	0.87
<i>RS (n = 3,660)</i>		
Quintile 1	Ref.	Ref.
Quintile 2	0.02 (–0.08, 0.12)	0.01 (–0.09, 0.11)
Quintile 3	0.06 (–0.04, 0.16)	0.04 (–0.06, 0.14)
Quintile 4	0.06 (–0.04, 0.15)	0.04 (–0.06, 0.14)
Quintile 5	0.06 (–0.04, 0.15)	0.06 (–0.04, 0.15)
<i>p</i> trend	0.19	0.27
<i>SENECA (n = 1,017)</i>		
Quintile 1	Ref.	Ref.
Quintile 2	0.00 (–0.19, 0.19)	–0.02 (–0.21, 0.18)
Quintile 3	0.25 (0.06, 0.45)	0.25 (0.05, 0.44)
Quintile 4	0.01 (–0.19, 0.20)	–0.01 (–0.20, 0.19)
Quintile 5	–0.12 (–0.31, 0.08)	–0.14 (–0.34, 0.06)
<i>p</i> trend	0.34	0.25

HDI, Healthy Diet Indicator; NHS, Nurses' Health Study; RS, Rotterdam Study; Ref., reference. Variables are mean differences (95% confidence interval). <sup>a</sup> Adjusted for age, gender, education, and study center (SENECA only). <sup>b</sup> Additionally adjusted for employment status, BMI, smoking status, energy intake, alcohol intake, physical activity, and depression.

and in a group of 1,651 Italian older men and women (odds ratio 0.85 [95% CI 0.77–0.93] [12]). Our study, using a much larger population, a prospective design, and the updated HDI guidelines, did not confirm previous findings.

The lack of significant associations could be a result of low variability in cognitive function as measured by the MMSE and TICS due to the ceiling effects of these tests. Future studies on cognitive functioning should preferably include tests that are able to measure areas of cognition most affected by common dementing illnesses, such as memory, attention, language and visuospatial abilities [33]. However, in our cohorts, we have observed associations between major risk factors and cognitive change based on TICS [34–38]. Two previous studies examining the initial HDI guidelines used the MMSE [13] and an extended and validated version of the MMSE, namely the 0- to 70-point neuropsychological test [12], to assess cognitive function. Although these tests are comparable to the tests that we used, the outcome was differently defined. We studied cognitive function and cognitive decline, whereas the previous studies evaluated cognitive impairment based on predefined cutoffs. This latter approach does not allow a distinction between initial level and change [33]. Furthermore, as our cohorts included relatively healthy, well-educated participants compared to the other populations [12, 13], it is possible that our participants reported healthy diets at baseline with an overall good cognitive functioning, limiting the ability to detect an association between the HDI and cognitive decline. Nonetheless, we had extremely high ability to identify even modest associations given our very large sample size. Previous studies used the initial HDI

including pulses and nuts, which were not part of the updated HDI. While we did not include nuts and pulses from the original HDI, the nutrients that would be neuroprotective from these foods, such as MUFAs, PUFAs, protein and fiber, would have been captured by the updated HDI, making it less likely that the omission of these 2 foods would explain the null findings.

Another point to consider is that due to the limited amount of dietary information across the 3 cohort studies, we included 7 out of 10 HDI components. However, we aimed to increase variability within the HDI score by using the recently developed continuous calculation system based on 7 dietary components (range 0–70 points) as proposed by Jankovic et al. [22]. It has been shown that using 7 components rather than 10 HDI components (where instead of polyunsaturated fat in the 7-component HDI model, n-3 PUFAs, n-6 PUFAs are used in addition to trans-fatty acids and sodium) resulted in less heterogeneity when studying the HDI in multiple cohort studies [22]. To test the effect of using 7 HDI components only compared to using 10 HDI components, we studied 10 HDI components in NHS and found similar null findings, indicating this probably does not explain our null findings.

Other dietary patterns that have been shown to be related to cognitive function and decline in European and American observational studies in older adults include the Mediterranean diet [17, 39–46], the Dietary Approaches to Stop Hypertension (DASH) diet [42, 44, 47], and the Healthy Eating Index (HEI) [45, 48]. Dietary intervention studies with the Mediterranean diet [30, 31] and the DASH diet [32] confirmed these findings. These food-based scores include high intakes of vegetables, fruits, legumes, whole grains, nuts, fish, MUFAs, PUFAs, moderate amounts of low-fat dairy products and alcohol and low amounts of red and processed meats, and the MUFA-to-saturated fats ratio.

More recently, dietary components linked to neuroprotection and cognitive function have been summarized into 1 dietary pattern score, namely the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet [49]. The MIND diet is a hybrid of the Mediterranean-DASH diets and includes high intakes of green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine and low amounts of red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food. This diet has been related to slower cognitive ageing in a single study of 960 older adults (mean age 81.4 years) of the Memory and Aging Project [49]. As the HDI does not include the majority of these components [8], or specific components shown to be associated with cognitive function, such as green leafy vegetables [36, 50] and berries [34], it could be that the HDI was well-designed to reduce the risk of chronic diseases in general, but not cognitive function. In contrast, the inclusion of very specific food items limits the possibility to jointly study effect estimates of multiple studies and to target multiple diseases at once by means of 1 dietary pattern, as does the HDI.

In stratified analyses, we observed less cognitive function decline with higher HDI scores in participants reporting a history of cardiovascular risk factors in SENECA. As the HDI has been developed to prevent chronic diseases, including hypertension, and as hypertension has been associated with a worse cognitive function [9–11], it was hypothesized that this group at high-risk for cognitive decline would benefit from a healthy diet such as the HDI. Biologically, the blood pressure-lowering effect of the HDI reduces thickening of the vessel wall, leading to less vascular narrowing, resulting in less thickening of the media and atheromatous plaques within larger cerebral arteries. This could result in a lower risk of rupture of these plaques which could cause complete occlusion of arteries and infarction of surrounding tissues [51].

The availability of harmonized dietary intake variables is a major strength of the present study. Furthermore, the use of harmonized outcome variables and covariates reduces heterogeneity. Additionally, 4 HDI components are expressed as energy percentage, increasing the comparability of diet between different cohorts using different dietary assessment methods.

Another advantage is the relatively long follow-up time of cognitive function with multiple repeated measures (NHS and SENECA 6 years, RS 10 years), which could have been sufficient to measure changes in cognitive function, as other studies were able to measure changes in cognitive function after 4–5 years of follow-up [39, 52]. Another strength is that we were able to study changes in cognitive function over time, allowing us to use all available data of all cohorts using a comparable measure across cohorts. Finally, studying dietary intake prior to the cognitive assessments including many years of follow-up minimized possible reverse causation.

It may be considered a limitation that we used 1 dietary intake assessment, assuming stable diets over time. Additional analyses confirmed that dietary intakes were similar over multiple time points in NHS and SENECA (data not shown). Furthermore, FFQs rely on participants' estimates of food intake, which can lead to misclassification of dietary pattern adherence. This is a common limitation of studies of diet, and our results from SENECA using a dietary history method did not result in different conclusions. Lastly, although we have tried to differentiate between a healthy lifestyle and a healthy diet by extensively adjusting for risk factors for cognitive decline, residual confounding remains possible due to unmeasured or imprecisely measured covariates.

We demonstrated that greater adherence to the WHO dietary guidelines for a healthy diet was not associated with reduced rates of cognitive decline in European and American older adults.

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### Disclosure Statement

The authors declare no conflict of interest.

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