Supplementary Appendix

Supplement to: Barnes LL, Dhana K, Liu X, et al. Trial of the MIND diet for prevention of cognitive decline in older persons. N Engl J Med 2022;387:602-11. DOI: 10.1056/NEJMoa2302368

This appendix has been provided by the authors to give readers additional information about the work.

Trial of the MIND diet for Prevention of Cognitive Decline in Older Persons

Supplementary Appendix

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List of Investigators

Lisa L. Barnes, PhD; Rush University Medical Center, Chicago, Illinois, US

Klodian Dhana, MD, PhD; Rush University Medical Center, Chicago, Illinois, US

Xiaoran Liu, PhD; Rush University Medical Center, Chicago, Illinois, US

Vincent J. Carey, PhD; Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Jennifer Ventrelle, MS; Rush University Medical Center, Chicago, Illinois, US

Kathleen Johnson, MPH; Harvard T.H. Chan School of Public Health, Boston, MA

Chiquia S. Hollings, MPH; Rush University Medical Center, Chicago, Illinois, US

Louise Bishop, MS, RD; Harvard T.H. Chan School of Public Health, Boston, MA

Nancy Laranjo, BA; Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Benjamin J. Stubbs, MS; Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Xavier Reilly, BS; Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Puja Agarwal, PhD; Rush University Medical Center, Chicago, Illinois, US

Shengwei Zhang, PhD; Rush University Medical Center, Chicago, Illinois, US

Francine Grodstein, ScD; Rush University Medical Center, Chicago, Illinois, US

Christy C. Tangney, PhD; Rush University Medical Center, Chicago, Illinois, US

Thomas M. Holland, MD, MS; Rush University Medical Center, Chicago, Illinois, US

Neelum T. Aggarwal, MD; Rush University Medical Center, Chicago, Illinois, US

Konstantinos Arfanakis, PhD; Rush University Medical Center, Illinois Institute of Technology, Chicago, Illinois, US

Martha Clare Morris, ScD (deceased); Rush University Medical Center, Chicago, Illinois, US

Frank M. Sacks, MD; Harvard T.H. Chan School of Public Health, Boston, MA

Study Population: Inclusion/Exclusion Criteria

Inclusion criteria.

- Men and women, 65-84 years of age
- Body Mass Index ≥ 25 kg/m²
- Willing to participate and give informed consent
- Family history of dementia, but without personal cognitive impairment (as measured by the MoCA > 22)[143, 144]
- Suboptimal diet (MIND score ≤8 out of 14)
- Eligible individuals must also agree not to take non-prescribed vitamin supplements, MVI or individual supplements of vitamin E, folic acid, n-3 fatty acids, or carotenoids.
- Physician prescribed supplements allowed
- Eligible individuals must not have a member of their household already enrolled in the Mind Diet Trial
- Successful completion of 3-4 week run-in period

Exclusion criteria.

- Medical History Exclusions
- Nuts, berries, olive oil, or fish allergies
- Use of medications to treat Alzheimer's disease or Parkinson's disease
- Psychosis or bipolar disorder
- Depression or other psychiatric disorder judged by study investigators to potentially interfere with participation
- Psychiatric medicines, reviewable by study investigators
- Report of alcohol or substance abuse within six months, or heavy alcohol consumption (>2 drinks/d women; >3 drinks/d men)
- Unstable or recent onset of cardiovascular disease, such as myocardial infarction within six months or presence of heart failure above type 1.
- Recent onset of stroke or transient ischemic attack (TIA), within three months
- Diagnosis of cancer within five years, except non-melanoma skin cancer (this criterion may be waived at the site PI's discretion)
- Illness that might be associated with weight change, such as a history of stomach or gastrointestinal conditions (Inflammatory Bowel Disease, Crohn's Disease, malabsorption, colostomy, bowel resection, gastric bypass surgery, etc.) (PI to use clinical judgment, and discuss exceptions with recruitment and steering committee)
- History of brain injury
- History of liver disease, HIV or Hepatitis C

1. How many times per week do you consume food from a fast food restaurant such as McDonald's, Burger King, Denny's, Dominos, Popeye's or Kentucky Fried Chicken? **____ per week**
2. How often do you consume sweets, candy bars, pastries, cookies or cakes per week? **____ per week**
3. How many servings of butter or stick margarine do you consume each day? (1 pat or teaspoon) **___tsp per day**
4. How many servings of whole fat or regular cheese or cream cheese do you eat each week? (1oz) **____ per wee**k
5. How many servings of red meat or processed meat, such as steak, ham, roast, hamburger, hot dogs or sausages do you consume each week? **____ per week**
6. How many servings of fish (not fried) do you consume each week? (3-5 oz) **____ per week**
7. How many servings of poultry such as chicken or turkey (not fried, skinless) do you consume each week? (3-5 oz**) ____ per week**
8. How many tablespoons of olive oil do you consume per day (including that used in salad dressings and cooking, sautéing, or on bread)? **____TB per day**
9. How many servings of green leafy vegetables do you eat each week, such as spinach, kale, greens, romaine? (1c for leafy, 1/2c for cooked/raw chopped) **____ per week**
10. How many servings (1/2 c) of other types of vegetables do you eat each week (e.g., broccoli, carrots, peas, onions, green/red peppers, celery, string beans, tomatoes, yams, squash, eggplant, etc.)? **____ per week**
11. How many servings (1/2c) of berries do you eat each week (e.g. strawberries, blueberries, raspberries)? **____ per week**
12. How many servings of beans/legumes (1/2 c) do you consume each week? **____ per week**
13. How many servings of whole grain breads, pasta, or cereals do you eat each day? (1 slice dark bread, ½ cup brown rice or pasta, ¾ cup whole grain cereal) **____ per day**
14. How many servings of nuts do you eat each week? (handful or ¼ cup) **____ per week**

MRI measures and post-processing procedures

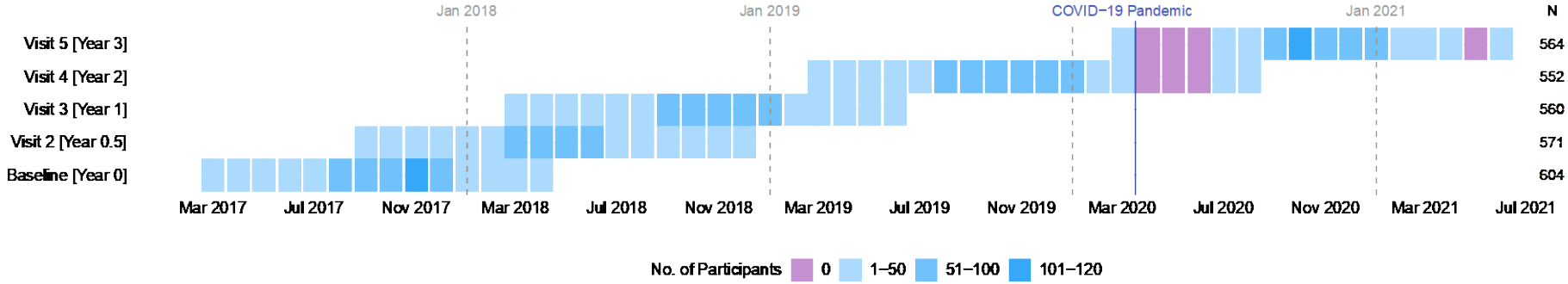
A secondary clinical outcome was change in MRI-derived measures of total brain volume, hippocampal volume, and volume of white matter hyperintense lesions. Imaging was conducted on a 3-Tesla Philips Achieva MRI scanner at the Chicago site and a Siemens Skyra MRI scanner at the Boston site. T1-weighted high-resolution anatomical data were collected with a 3D magnetization-prepared rapid acquisition gradient echo sequence and the following parameters for Philips: TE = 3.7 ms, TR= 8.1 ms, inversion time= 962 ms, flip angle 8°, 181 sagittal slices, acquired voxel-size of 1 mm^3, parallel imaging acceleration factor of 2; for Siemens: TE = 3 ms, TR= 2.3 s, inversion time= 900 ms, flip angle 9°, 176 sagittal slices, acquired voxel-size of 1 mm^3, parallel imaging acceleration factor of 2. T2-weighted fluid-attenuated inversion recovery (FLAIR) data were collected with a fast spin-echo (FSE) sequence and the following parameters for Philips: TE = 90 ms, TR = 9 s, inversion time TI = 2.5 s, 35 axial slices, acquired voxel-size of 3.9 mm^3; for Siemens: TE = 152 ms, TR = 9 s, inversion time TI = 2.5 s, 35 axial slices, acquired voxel-size of 3.2 mm^3.

MRI data from each scan of each participant underwent post-processing as follows. T1-weighted data were segmented using the Computational Anatomy Toolbox (CAT12)[1] and the tissue masks were used as priors for N4 bias field correction.[2] The total gray and white matter volume was computed and normalized by the total intracranial volume. FreeSurfer[3] was used to segment the left and right hippocampus and the average hippocampal volume was computed and normalized by the total intracranial volume. The T1-weighted and FLAIR data from each participant were rigidly aligned and used to segment white matter hyperintense (WMH) lesions.[4] The total volume of WMH lesions was normalized by the total intracranial volume, multiplied by 1000 and transformed by the logarithm base 10.

Shutdown of trial activities during COVID pandemic.

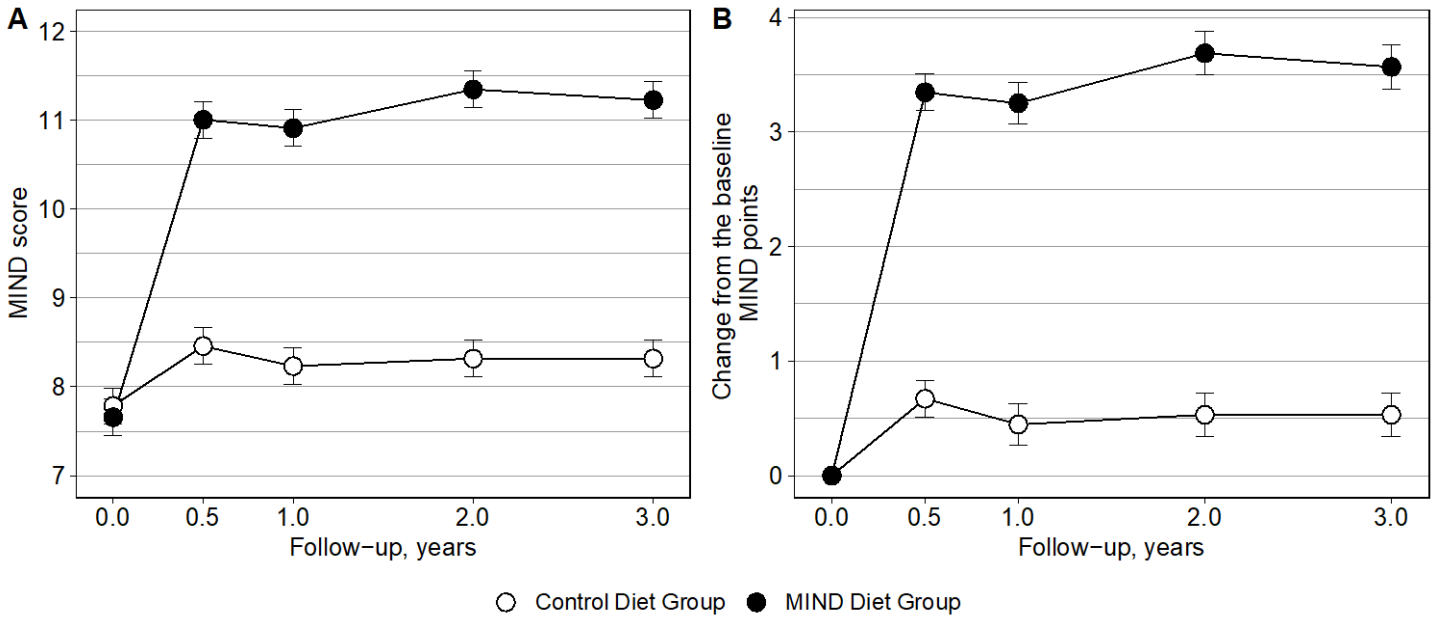
Due to the COVID19 pandemic, in-person research was suspended in March 2020 and resumed in mid-July 2020 following institutional-specific guidelines for COVID safety (Supplementary Figure 1). Year 2 outcome assessments were completed on 533 persons before the shutdown. Once in-person testing resumed, only cognitive function and physical measurements (e.g., blood draw, blood pressure, waist circumference, and weight) were collected to limit exposure to less than 1.5 hours, and all other covariate data were collected via telephone. Videos were created to share content as a substitute for group sessions and food was either delivered or shipped to participants depending on preference. The MRI facilities were limited to clinical activities for several months and once re-opened priority was given to participants who completed a baseline scan prior to the pandemic at each site. An extension of 3 months was added to the study period to accommodate the shutdown during which time remaining participants continued to receive telephone diet counseling. Forty-four participants declined in-person testing for month 36 and instead received a subset of cognitive tests via telephone.

Figure S1: Cognitive assessment by calendar and follow-up time in the MIND trial



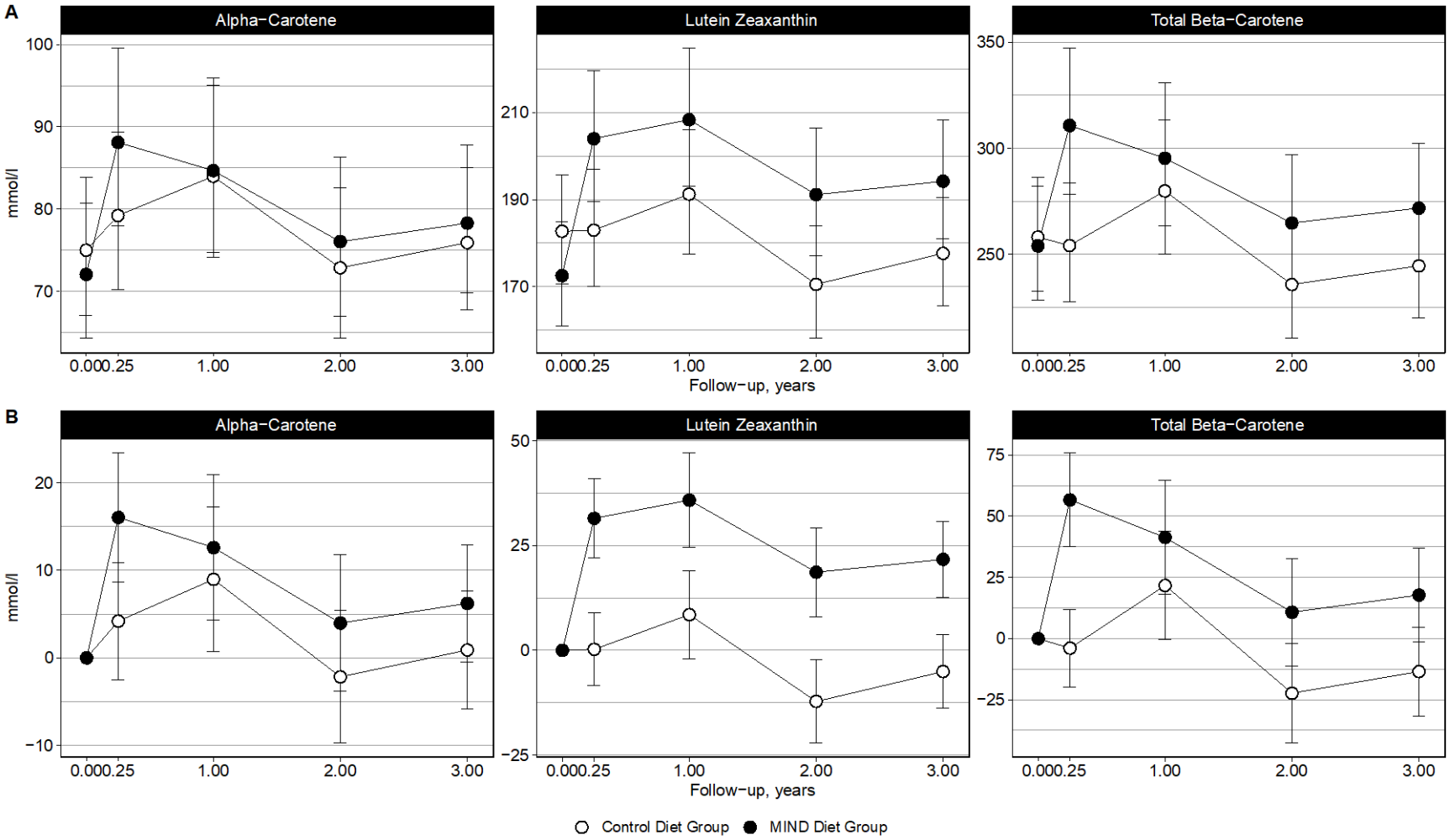
During COVID-19 pandemic, we temporarily halted trial operations from March 19, 2020, to July 15, 2020.

Figure S2: Fitted mean of the MIND diet score in the MIND diet group and control diet group.



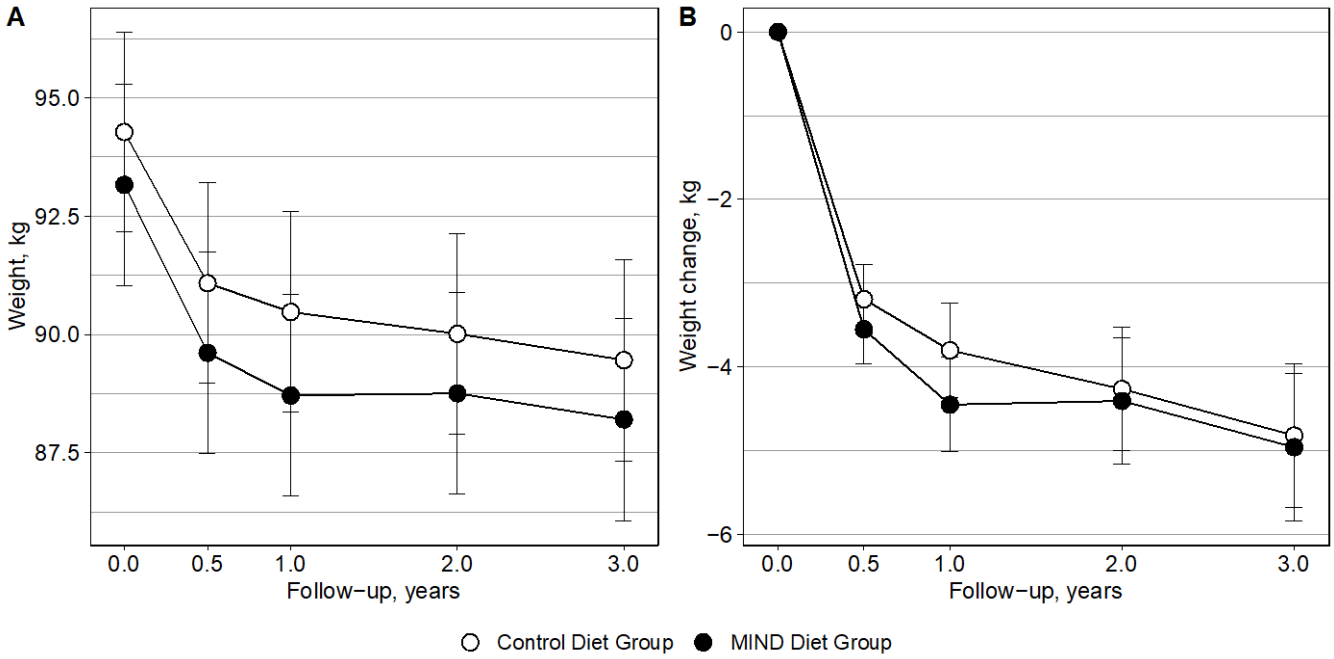
A. Mean (95%CI) of MIND score at the baseline and month 6, year 1, year 2, and year 3.
B. Change (difference) and 95%CI of MIND score from the baseline to month 6, year 1, year 2, and year 3.

Figure S3: Fitted mean of antioxidants levels in the MIND diet group and control diet group.



A. Mean (95%CI) of Alpha-Carotene, Lutein Zeaxanthin, and Total Beta-Carotene in blood at the baseline month 3, year 1, year 2, and year 3.
B. Change (difference) and 95%CI of Alpha-Carotene, Lutein Zeaxanthin, and Total Beta-Carotene from the baseline to month 3, year 1, year 2, and year 3.

Figure S4: Fitted mean of body weight in the MIND diet group and control diet group.



A. Mean (95%CI) of body weight (kg) at the baseline, month 6, year 1, year 2, and year 3.

B. Change (difference) and 95%CI of body weight (kg) from the baseline to month 6, year 1, year 2, and year 3.

Table S1: Effect of the MIND diet intervention on imputed global cognition during 3 years of follow-up

	Dietary Assignment				
	Control Diet		MIND Diet		
No. of Years Since Randomization	**No. of individuals**	**Change from the baseline, Estimated Mean (95%CI)**	**No. of individuals**	**Change from the baseline, Estimated Mean (95%CI)**	**Difference between interventions, MIND vs Control, Beta (95%CI)**
0.0	303	0 (reference)	301	0 (reference)	
0.5	303	0.118 (0.087 to 0.150)	301	0.124 (0.092 to 0.155)	0.005 (-0.039 to 0.050)
1.0	303	0.212 (0.172 to 0.251)	301	0.226 (0.186 to 0.266)	0.015 (-0.041 to 0.070)
2.0	303	0.200 (0.155 to 0.244)	301	0.245 (0.201 to 0.289)	0.045 (-0.018 to 0.108)
3.0	303	0.171 (0.124 to 0.217)	301	0.201 (0.153 to 0.249)	0.030 (-0.036 to 0.097)

Abbreviations: MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; n, Number of participants; CI, confidence interval.

Table S2: Effect of the MIND diet intervention on global cognition during 3 years of follow-up (excluding cognitive assessments obtained through phone)

	Dietary Assignment				
	Control Diet		MIND Diet		
No. of Years Since Randomization	**No. of individuals**	**Change from the baseline, Estimated Mean (95%CI)**	**No. of individuals**	**Change from the baseline, Estimated Mean (95%CI)**	**Difference between interventions, MIND vs Control, Beta (95%CI)**
0.0	303	0 (reference)	301	0 (reference)	
0.5	287	0.117 (0.086 to 0.149)	284	0.125 (0.093 to 0.157)	0.008 (-0.037 to 0.053)
1.0	281	0.212 (0.176 to 0.248)	279	0.226 (0.189 to 0.262)	0.013 (-0.038 to 0.064)
2.0	282	0.202 (0.165 to 0.239)	270	0.245 (0.207 to 0.283)	0.043 (-0.010 to 0.096)
3.0	269	0.179 (0.141 to 0.217)	251	0.206 (0.167 to 0.245)	0.027 (-0.027 to 0.082)

Abbreviations: MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; n, Number of participants; CI, confidence interval.

Table S3: Effect of the MIND diet intervention on individual cognitive domains during 3 years of follow-up

	Dietary Assignment				
	Control Diet		MIND Diet		
No. of Years Since Randomization	No. of individuals	Change from the baseline, Estimated Mean (95%CI)	No. of individuals	Change from the baseline, Estimated Mean (95%CI)	Difference between interventions, MIND vs Control, Beta (95%CI)
Episodic memory					
0.0	303	0 (reference)	301	0 (reference)	
0.5	287	0.170 (0.112 to 0.228)	284	0.159 (0.100 to 0.217)	-0.012 (-0.094 to 0.070)
1.0	281	0.256 (0.193 to 0.32)	279	0.293 (0.229 to 0.357)	0.037 (-0.053 to 0.127)
2.0	282	0.255 (0.190 to 0.319)	270	0.295 (0.229 to 0.36)	0.040 (-0.052 to 0.132)
3.0	289	0.232 (0.168 to 0.296)	275	0.277 (0.211 to 0.342)	0.045 (-0.046 to 0.137)
Executive function					
0.0	303	0 (reference)	301	0 (reference)	
0.5	286	0.103 (0.045 to 0.161)	284	0.074 (0.016 to 0.132)	-0.029 (-0.111 to 0.053)
1.0	280	0.138 (0.071 to 0.205)	279	0.122 (0.055 to 0.189)	-0.016 (-0.111 to 0.079)
2.0	282	0.121 (0.051 to 0.191)	270	0.168 (0.096 to 0.240)	0.047 (-0.053 to 0.147)
3.0	268	0.071 (-0.001 to 0.143)	251	0.141 (0.067 to 0.214)	0.070 (-0.033 to 0.173)
Perceptual speed					
0.0	303	0 (reference)	301	0 (reference)	
0.5	287	0.017 (-0.037 to 0.071)	284	0.098 (0.044 to 0.152)	0.081 (0.004 to 0.157)
1.0	281	0.175 (0.116 to 0.233)	279	0.227 (0.169 to 0.286)	0.053 (-0.030 to 0.136)
2.0	282	0.186 (0.127 to 0.245)	270	0.243 (0.183 to 0.303)	0.057 (-0.027 to 0.141)
3.0	269	0.125 (0.065 to 0.185)	251	0.134 (0.072 to 0.195)	0.008 (-0.078 to 0.094)
Semantic memory					
0.0	303	0 (reference)	301	0 (reference)	
0.5	287	0.146 (0.088 to 0.205)	284	0.142 (0.084 to 0.200)	-0.005 (-0.087 to 0.078)
1.0	281	0.229 (0.162 to 0.296)	279	0.167 (0.100 to 0.235)	-0.062 (-0.157 to 0.034)
2.0	282	0.174 (0.103 to 0.244)	270	0.201 (0.129 to 0.273)	0.027 (-0.073 to 0.128)
3.0	289	0.207 (0.137 to 0.277)	275	0.164 (0.092 to 0.236)	-0.043 (-0.144 to 0.057)

Abbreviations: MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; n, Number of participants; CI, confidence interval.

Supplemental Table 4: Serious Adverse Events by Diet Arm and Overall			
	Control Diet N_1 = 91* (n_2=153)	MIND Diet N_1 = 89* (n_2=127)	All N_1 = 180* (n_2=280)
Cancer	11 (19)	8 (10)	19(29)
Cardiovascular	23 (32)	16 (17)	39 (49)
Endocrine	3 (3)	1 (1)	4 (4)
Gastrointestinal	10 (11)	10 (10)	20 (21)
Genitourinary-Reproductive	4 (4)	4 (4)	8 (8)
Infectious	18 (26)	16 (18)	34 (44)
Musculoskeletal	26 (29)	34 (39)	60 (68)
Neurological	11 (13)	14 (18)	25 (31)
Other	6 (8)	4 (4)	10 (12)
Pulmonary	6 (6)	1 (1)	7 (7)
Renal	2 (2)	2 (2)	4(4)
Unknown	0(0)	3(3)	3(3)

n_1 = number of individual participants *per SAE*

n_2 = number of distinct SAE

*The number of participants with at least one SAE is 180. The total number of SAE's is 280 due to some individuals having multiple SAEs in multiple categories

Supplemental Table 5 on Representativeness of Study Participants.

Category	
Condition under investigation	Cognitive decline
Special considerations related to	
Age	Prevalence increases after age 65 years
Race and ethnicity	Black and Latino adults are at greater risk
Sex and gender	Women may be at greater risk due to longer longevity
Other considerations	
Apolipoprotein E4 allele	Those with one or two e4 alleles have faster rates of cognitive decline
Overall representativeness of this trial	Trial was not representative of population most at risk for Alzheimer's disease

Information for this table is based on the general epidemiologic literature in the Alzheimer's field.

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