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Structured vs Self-Guided Multidomain Lifestyle Interventions for Global Cognitive Function
The US POINTER Randomized Clinical Trial

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IMPORTANCE Identifying new interventions to slow and prevent cognitive decline associated with dementia is critical. Nonpharmacological interventions targeting modifiable risk factors are promising, relatively low-cost, accessible, and safe approaches.

OBJECTIVE To compare the effects of two 2-year lifestyle interventions on cognitive trajectory in older adults at risk of cognitive decline and dementia.

DESIGN, SETTING, AND PARTICIPANTS Single-blind, multicenter randomized clinical trial enrolling 2111 participants from May 2019 to March 2023 (final follow-up, May 14, 2025) at 5 clinical sites in the US. Participant inclusion criteria enriched risk of cognitive decline and included age 60 to 79 years, sedentary lifestyle, and suboptimal diet plus at least 2 additional criteria related to family history of memory impairment, cardiometabolic risk, race and ethnicity, older age, and sex.

INTERVENTIONS Participants were randomly assigned with equal probability to structured (n = 1056) or self-guided (n = 1055) interventions. Both interventions encouraged increased physical and cognitive activity, healthy diet, social engagement, and cardiovascular health monitoring, but differed in structure, intensity, and accountability.

MAIN OUTCOMES AND MEASURES The primary comparison was difference between intervention groups in annual rate of change in global cognitive function, assessed by a composite measure of executive function, episodic memory, and processing speed, over 2 years.

RESULTS Among the 2111 individuals enrolled (mean age, 68.2 [SD, 5.2] years; 1455 [68.9%] female), 89% completed the year 2 assessment. The mean global cognitive composite *z* score increased from baseline over time in both groups, with a mean rate of increase per year of 0.243 SD (95% CI, 0.227-0.258) for the structured intervention and 0.213 SD (95% CI, 0.198-0.229) for the self -guided intervention. The mean rate of increase per year was statistically significantly greater for the structured group than the self-guided group by 0.029 SD (95% CI, 0.008-0.050; *P* = .008). Based on prespecified secondary subgroup comparisons, the structured intervention benefit was consistent for *APOE* ε4 carriers and noncarriers (*P* = .95 for interaction) but appeared greater for adults with lower vs higher baseline cognition (*P* = .02 for interaction). Fewer ascertained adverse events were reported in the structured group (serious: 151; nonserious: 1091) vs the self-guided group (serious: 190; nonserious: 1225), with a positive COVID-19 test result being the most common adverse event overall and more frequent in the structured group.

CONCLUSIONS AND RELEVANCE Among older adults at risk of cognitive decline and dementia, a structured, higher-intensity intervention had a statistically significant greater benefit on global cognition compared with an unstructured, self-guided intervention. Further investigation of functional outcomes, biomarkers, and ongoing extended follow-up will help address clinical relevance and sustainability of the observed cognitive benefits.

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Visual Abstract
Editorial page 674
Supplemental content

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Identifying efficacious interventions to slow or prevent cognitive decline associated with Alzheimer disease (AD) and related dementias is a major public health priority due to the growing number of affected individuals and the profound economic, psychological, and social burdens of the disease.[1] Late-life cognitive decline is often attributable to mixed pathology,[2] and effective treatment will likely require a multipronged therapeutic strategy to address multiple mechanisms associated with AD and vascular disease, among others. Thus, there is a critical need for interventions that target several risk pathways simultaneously. Recent advances in antiamyloid therapeutics show evidence for slowing of AD-specific clinical progression.[3-5] These treatments are approved for individuals with confirmed AD pathology, specifically those with mild cognitive impairment or mild dementia and a positive amyloid biomarker.[6] Although they have been shown to effectively remove β-amyloid, they do not address vascular pathologies such as infarcts and arteriolosclerosis that increase risk of cognitive decline and dementia and that are highly prevalent in older adult populations. There remains a significant need for better treatments and for therapies that can impact AD and related dementias more broadly.

Nonpharmacological strategies targeting modifiable risk factors offer a promising, low-cost, accessible, and safe approach. The latest *Lancet* Commission report on dementia prevention[7] identified 14 modifiable risk factors that, if addressed, could potentially reduce dementia incidence by 45%. Multidomain lifestyle interventions addressing multiple pathways have proliferated since the landmark 2015 Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER).[8] FINGER demonstrated significant cognitive benefit after 2 years of multidomain intervention in older adults at elevated risk of AD and related dementias. The World-Wide FINGERS (WW-FINGERS) network was launched in 2017 to foster global collaboration, protocol alignment, and data sharing across nonpharmacological risk reduction trials.[9] Additional multidomain lifestyle trials have been conducted,[10-17] although some have not demonstrated benefit.[13-16] Differences in trial protocols (eg, sample, intervention intensity, participant support, outcomes) likely explain variability and underscore the need for harmonization.[18]

The US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER) was developed to assess whether FINGER results generalize to a larger, more diverse US population at risk of dementia, using culturally adapted protocols.[19] The primary aim of this randomized 2-year clinical trial was to compare the effects of 2 multimodal lifestyle interventions on global cognitive function in 2000 at-risk older adults.

Key Points

Question Can multidomain lifestyle interventions improve or protect cognitive function in older adults at risk of cognitive decline and dementia?

Findings In this randomized clinical trial of 2111 older adults at risk of cognitive decline and dementia, a structured lifestyle intervention of regular moderate- to high-intensity physical exercise, adherence to the MIND diet, cognitive challenge and social engagement, and cardiovascular health monitoring led to a statistically significant greater improvement in global cognition over 2 years relative to a lower-intensity self-guided intervention (mean composite *z*-score increase of 0.243 SD per year vs 0.213 SD per year, respectively).

Meaning The structured, higher-intensity intervention had a greater benefit on global cognition than the self-guided, low-intensity intervention. Further research is needed to understand clinical significance and longer-term cognitive effects of both interventions.

Methods

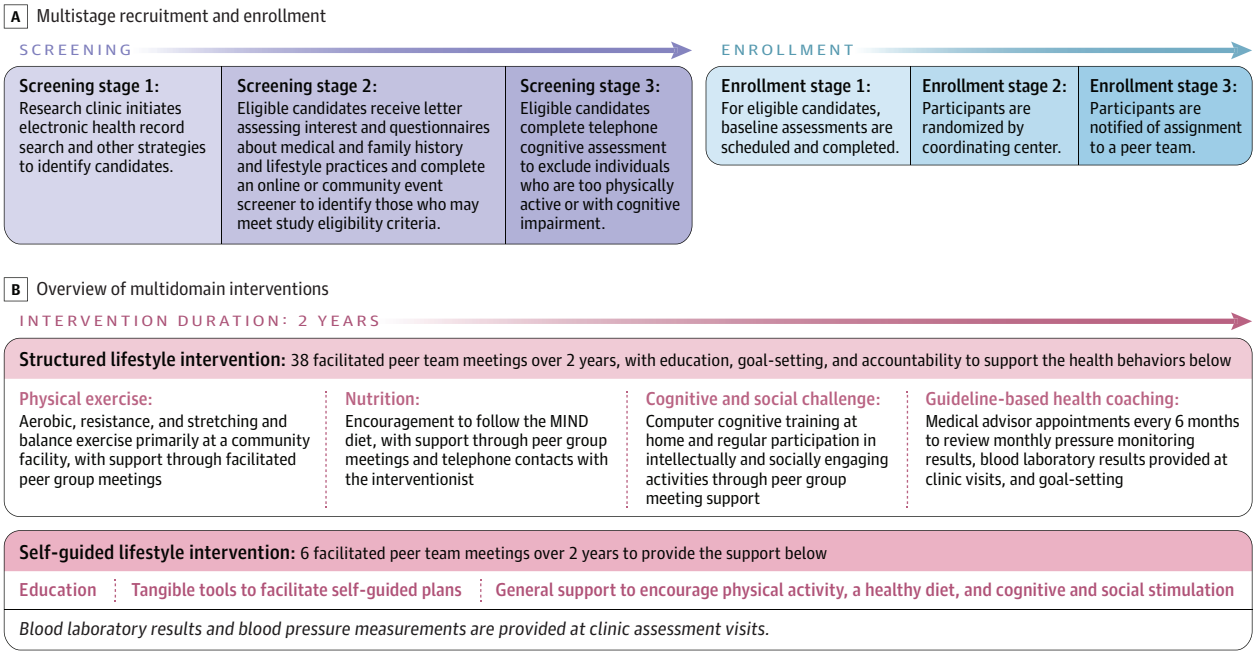
Trial Design and Oversight

The study design and methods are published,[19] and the trial protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively. An overview of screening, enrollment, and the interventions is provided in Figure 1. US POINTER was a phase 3, 5-site, 2-year, single-blind randomized clinical trial of 2 lifestyle interventions in older adults at risk of dementia due to established demographic, lifestyle, family history, and cardiometabolic factors.[20] A central institutional review board at Wake Forest University School of Medicine approved the study. All participants provided written informed consent. The trial was conducted in accordance with established ethical standards. An external, independent data and safety monitoring board provided safety oversight. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for nonpharmacological trials.[21]

Participants

Participants were recruited via electronic health records and grassroots engagement leveraging local community partnerships for assistance.[19] Eligibility criteria were designed to identify cognitively asymptomatic older adults at elevated risk of cognitive decline and dementia.[19] Participants were 60 to 79 years old, were sedentary (per the modified Telephone Assessment of Physical Activity: less than 60 minutes per week at moderate intensity), and had a suboptimal diet (Mediterranean-DASH Intervention for Neurodegenerative Delay [MIND] diet screener: ≤9 of 14 points), plus 2 of the following: first-degree family history of memory impairment; elevated cardiometabolic risk (systolic blood pressure ≥125 mm Hg, low-density lipoprotein cholesterol ≥115 mg/dL [2.98 mmol/L], or hemoglobin A_{1c} ≥6.0%); self-identified American Indian or Alaska Native, Black, African American, or African, or Middle Eastern or North African race; Hispanic, Latinx, or Spanish ethnicity; age 70 to 79 years; or male sex. Race and ethnicity were self-reported via questionnaire, allowing multiple fixed-category selections, including "none of the above describes me," which was coded as "other." This information was collected to support the study objective of enhancing generalizability through enrollment of a diverse and representative cohort. Key exclusions included

Figure 1. Recruitment and Enrollment Stages of US POINTER and Overview of Multidomain Interventions



Recruitment relied on a 3-stage process (panel A) that included outreach through electronic health records, site registries, and community partners to engage interested individuals (screening stage 1), who then received mailed study information and hard-copy or online questionnaires to assess eligibility (screening stage 2). Screening stage 3 was completed by telephone for cognitive screening and to confirm sedentary status. The 3-stage enrollment process included baseline assessment to confirm eligibility (enrollment stage 1), randomization (enrollment stage 2), and participants are notified of peer team assignment (enrollment stage 3). Panel B provides an overview of activities and expectations for the structured and self-guided intervention groups. MIND indicates Mediterranean-DASH Intervention for Neurodegenerative Delay.

neurological/psychiatric disorders, significant systemic disease, use of cognition-altering medications, or cognitive impairment (modified Telephone Interview for Cognitive Status score <32; Clinical Dementia Rating [CDR] global score >0.5 and CDR sum of box scores >1). Participants were willing to be randomized and attend community-based intervention group meetings.

Trial Procedures

Eligibility was determined via mailed outreach, phone screening, and in-person visits (Supplement 1).[19] Clinic assessments, including blood collection and medical review, were completed at baseline and every 6 months for 2 years. Participants could join ancillary studies of brain imaging,[22] home-based sleep assessments,[23] peripheral/neurovascular assessments,[24] and gut microbiome analyses.

Randomization and Masking

Randomization was stratified by site using a centrally generated, variable-length algorithm in blocks of 4 or 6, securely embedded in the study database. Only data coordinating center personnel, the intervention oversight committee, and relevant site staff (intervention teams, study clinicians) were unmasked to intervention assignment. All team members were masked to outcome data except site staff responsible for assessments or data entry, the lead neuropsychologist and outcomes project manager, and the data coordinating center. Masked personnel had restricted database access and were excluded from unmasking discussions. Participants were reminded at clinic visits to avoid disclosing group assignment. Masking procedures were effective; only 1 examiner was unmasked to a participant's group assignment. No interim outcomes analyses by intervention assignment were conducted before initiation of study closeout.

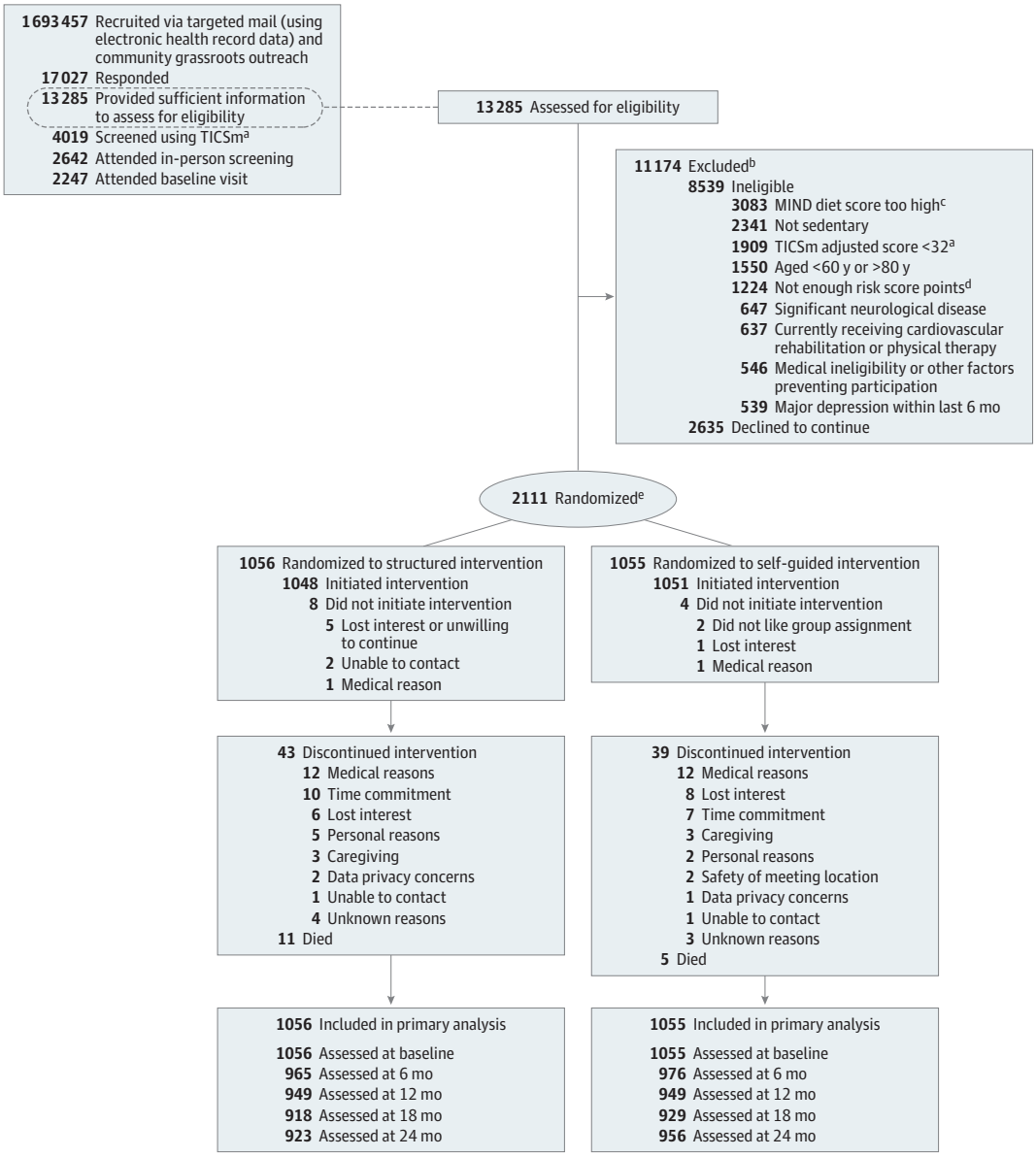
Interventions

Intervention details are published[19] and described in the trial protocol (Supplement 1). An overview is provided in Figure 1. Both interventions promoted increased physical and cognitive activity, healthy diet, social engagement, and cardiovascular monitoring but differed in structure, intensity, and accountability. Participants were randomized 1:1 to the structured or self-guided intervention (**Figure 2**) and assigned to peer teams (10-15 participants) for support. Navigators from the Alzheimer's Association supported both groups. Structured group teams received additional support from certified interventionists.

Structured Lifestyle Intervention

The structured group attended 38 facilitated team meetings over 2 years with structured intervention navigators and interventionists and received activity plans with quantifiable adherence metrics (Supplement 1). The intervention included aerobic (4 days per week, 30-35 minutes per session), resistance (2 days per week, 15-20 minutes per session), and flexibility (2 days per week, 10-15 minutes per session) training, primarily at a community facility (eg, YMCA); guidelines for

Figure 2. Participant Flow in US POINTER



[a]The modified Telephone Interview for Cognitive Status (TICSm) is a test of global cognitive function with a range of 0 to 50, with higher scores reflecting better cognition. Participants scoring >32 were deemed cognitively eligible.

[b]Potential participants could be ineligible for more than 1 reason. Only reasons that excluded ≥500 persons are shown.

[c]The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet screener scores range from 0 to 14 and assess consumption of food groups linked to cognitive health in older adults. Scores ≤9.0, indicating suboptimal adherence, were required for study eligibility.

[d]The risk score for cognitive decline was based on having a sedentary lifestyle (1 point; Telephone Assessment of Physical Activity, <60 min/wk at moderate intensity); having a suboptimal diet (1 point; MIND diet screener score ≤9); and at least 2 of the following: first-degree family history of memory impairment (1 point); elevated cardiometabolic risk (1 point; systolic blood pressure ≥125 mm Hg, low-density lipoprotein cholesterol ≥115 mg/dL [2.98 mmol/L], or hemoglobin A_{1c} ≥6.0%); self-identified American Indian or Alaska Native, Black, African American, or African, or Middle Eastern or North African race or Hispanic, Latinx, or Spanish ethnicity (1 point); age 70 to 79 years (1 point); or male sex (1 point).

[e]Randomization was stratified by clinical site.

following the MIND diet (components listed in eTable 1 in Supplement 3); weekly web-based cognitive training using BrainHQ (3 times per week, 15-20 minutes per session); and biannual review of abnormal laboratory results (blood pressure, cholesterol, hemoglobin A_{1c}) with reinforcement of intervention goals. Monthly rebates of up to $10 for purchase of blueberries were offered to participants in the structured lifestyle intervention group.

Self-Guided Lifestyle Intervention

The self-guided group received publicly available education materials and was encouraged to make lifestyle changes that

best suited personal needs and schedules. Gift cards ($75) were provided at team meetings to support behavior change. Self-guided intervention navigators offered encouragement, without goal-directed coaching, during 6 peer team meetings held over 2 years. Annual guideline-based health monitoring was conducted during clinic visits.

Outcomes

The primary outcome was a global cognitive composite score, constructed from equally weighted domain composites of executive function, episodic memory, and processing speed—domains previously shown to improve with multidomain lifestyle interventions.[8,12] Composite scores are more sensitive to subtle cognitive changes in cohorts whose cognition is largely intact but who are at risk of cognitive decline,[25,26] and these scores provide greater statistical power than individual test scores.[27] The 3 domain composites, which served as prespecified secondary outcomes, were derived from tests of the modified Neuropsychological Test Battery,[28] which include the Free and Cued Selective Reminding Test (FCSRT), Story Recall, Visual Paired Associates, Number Span, Word Fluency, Trail-Making Test Parts A and B (TMT-A and TMT-B), and Digit Symbol Substitution Test (DSST). The domain composites of executive function (Number Span, Fluency, TMT-B), episodic memory (FCSRT, Story Recall, Visual Paired Associates), and processing speed (TMT-A, DSST) were constructed from *z*-transformed test scores (see Supplement 2 for scoring details). Assessments were administered during clinic visits at baseline and every 6 months for 2 years.

The trial protocol (Supplement 1) specifies additional secondary outcomes—including other cognitive measures, functional outcomes, and self-reported lifestyle activities—that will be reported in future publications.

Adjudication of Baseline Cognitive Status

Participants with baseline CDR scores of 0.5 or Mini-Mental State Examination scores of 26 or lower were flagged for central adjudication of possible mild cognitive impairment or AD and related dementias by an expert panel. Review materials included baseline cognitive test scores, questionnaires about cognitive concerns and depression, relevant medical and medication histories, and responses on the CDR. If a study partner was unavailable, the study clinician provided input on CDR global score. Each case was discussed until the panel majority agreement was reached on 1 of the following: no cognitive impairment, mild cognitive impairment, probable dementia, or cannot classify.

Sample Size

The target enrollment (n = 2000) with 2 years of follow-up provided at least 85% power at a 2-sided α = .05 to detect an 0.030-SD per-year difference in slopes (based on FINGER results[8]) for the primary outcome. Simulations of cognitive trajectories in the Women's Health Initiative Study of Cognitive Aging[29] were used to project power (Supplement 2). One interim analysis (pooled across intervention groups) confirmed assumptions about variances, longitudinal correlations, and missing data. As the interim analysis was masked to group assignment, no type I error penalty was applied.

Safety

Adverse events were ascertained at 6-month clinic visits using a standardized query by unmasked assessors. Events could also be spontaneously reported (volunteered) between visits to site staff or intervention personnel. If reported both ways, events were coded as ascertained. The *Medical Dictionary for Regulatory Activities* (*MedDRA*) was used for coding (up to 3 codes per event) by the data coordinating center. The masked trial safety officer and unmasked site clinicians assessed relationship to the intervention.

Serious adverse events were defined as fatal/life-threatening, causing disability, requiring hospitalization, or deemed clinically significant by investigators. Prespecified conditions of interest—such as injurious falls, fractures, musculoskeletal pain, gastrointestinal symptoms, and COVID-19 test result positivity—were reported as nonserious adverse events (eTable 2 in Supplement 3).

Statistical Analysis

All data from all participants were analyzed according to intervention assignment. Results are reported as point estimates (mean differences across groups) and 95% confidence intervals. Test scores were converted to *z* scores using the baseline mean and standard deviation. Composite scores were the mean of individual test *z* scores renormalized to a standard deviation of 1 at baseline. See Supplement 2 for more details.

Trajectories of change in cognitive *z* scores from baseline were portrayed using linear contrasts from a mixed-effects model for repeated measures.[22] Repeated test administration is known to produce practice effects, in which scores may initially improve and then plateau or decline with subsequent testing. The primary inference model included covariate adjustment to account for these effects and the possibility that practice effects varied by age.

Time (clinic visit) in the primary inference was coded as 0, 0.5, 1.0, 1.5, and 2.0 years and treated as a continuous variable, with values assigned that best aligned with the scheduled clinic visits (ie, baseline and months 6, 12, 18, and 24). Independent variables included participant, intervention assignment, time, site (stratification factor), baseline age, test version (if more than 1 version was used), a counter for number of prior assessments (ie, 0, 1, 2, 3, etc, to control for practice effects), and a counter × age interaction. Missing data were assumed to be missing at random. Two-tailed type I error was set at .05. An intervention × time interaction tested whether covariate-adjusted slopes differed between groups (as in FINGER[8]). Models used restricted maximum likelihood with an unstructured covariance. Inverse probability weighting was used to assess the impact of missing data, and post hoc supporting analyses evaluated the sensitivity of results to model assumptions (eAppendix 1 in Supplement 3).

Consistency of effects across domain composites for episodic memory, executive function, and processing speed were examined using similar models as prespecified secondary outcomes in the statistical analysis plan, and results are reported with 95% confidence intervals. Prespecified secondary

Table 1. Baseline Participant Characteristics

Characteristics	Structured (n = 1056)	Self-guided (n = 1055)
Age, mean (SD), y	68.3 (5.2)	68.1 (5.2)
Aged ≥75 y, No. (%)	143 (13.5)	131 (12.4)
Sex, No. (%)		
Female	721 (68.3)	734 (69.6)
Male	335 (31.7)	321 (30.4)
Race and ethnicity, No. (%)[a]		
American Indian or Alaska Native	3 (0.3)	1 (0.1)
Asian or Asian American	33 (3.1)	22 (2.1)
Black, African American, or African	161 (15.2)	179 (17.0)
Hispanic, Latinx, or Spanish	63 (6.0)	61 (5.8)
Middle Eastern or North African	1 (0.1)	1 (0.1)
White or European American	725 (68.7)	729 (69.1)
Multiple	55 (5.2)	51 (4.8)
Other	10 (0.9)	6 (0.6)
Prefer not to respond	5 (0.5)	5 (0.5)
Highest level of education, No. (%)		
High school	54 (5.1)	56 (5.4)
Some college/associate's degree	257 (24.5)	268 (25.6)
Bachelor's degree	352 (33.6)	372 (35.6)
Postgraduate degree	386 (36.8)	349 (33.4)
Body mass index, median (IQR)[b]	30.0 (26.0-33.3)	30.0 (25.9-33.4)
Blood pressure, mean (SD), mm Hg		
Systolic[c]	131.5 (15.9)	130.7 (16.0)
Diastolic[d]	76.8 (9.4)	76.6 (9.4)
Hemoglobin A_{1c}, mean (SD), %[e]	5.9 (0.7)	5.9 (0.7)
Cholesterol, mean (SD), mg/dL		
Total[f]	192.7 (42.5)	194.7 (42.6)
LDL-C[g]	111.6 (36.0)	113.1 (36.2)
FRS CVD risk and prevalence, No. (%)[h]		
Low (<10%)	289 (27.4)	331 (31.4)
Medium (10%-20%)	344 (32.6)	334 (31.7)
High (>20%)	261 (24.7)	268 (25.4)
Prevalent cardiovascular disease	162 (15.3)	119 (11.3)
APOE ε4 carrier, No. (%)[i]	322 (30.6)	338 (32.2)
Family history of memory loss, No. (%)	837 (79.3)	836 (79.2)
MIND diet score, mean (SD)[j]	7.0 (1.4)	7.1 (1.4)
TICSm score, mean (SD)[k]	37.6 (3.4)	37.6 (3.2)
MMSE score, median (IQR)[l]	29 (28-30)	29 (28-30)
Geriatric Depression Scale score, median (IQR)[m]	1 (0-2)	1 (0-3)
Adjudicated mild cognitive impairment, No. (%)[n]	52 (4.9)	47 (4.5)

SI conversion: To convert total cholesterol and LDL-C to millimoles per liter, multiply by 0.0259.

[a] Race and ethnicity were self-identified by participants on a questionnaire, and multiple selections were permitted. If a participant indicated "none of the above describes me," race and ethnicity were coded as "other."

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared: overweight was defined as 25 to 29.9; obese, ≥30.0.

[c] Elevated systolic blood pressure was defined as ≥130 mm Hg.

[d] Elevated diastolic blood pressure was defined as ≥80 mm Hg.

[e] Elevated hemoglobin A_{1c} was defined as >5.6%.

[f] Elevated total cholesterol was defined as ≥200 mg/dL.

[g] Elevated low-density lipoprotein cholesterol (LDL-C) was defined as ≥100 mg/dL.

[h] Cardiovascular disease (CVD) risk was estimated using the Framingham risk score (FRS) to identify low (<10%), medium (10%-20%), and high (>20%) risk based on D'Agostino et al.[30] Prevalent CVD describes participants who reported myocardial infarction, cardiac arrest, congestive heart failure, uncontrolled arrhythmia, uncontrolled angina, stent placement, angioplasty, coronary artery bypass graft surgery, valve replacement, deep vein thrombosis or pulmonary embolism, stroke, or transient ischemic attack at baseline.

[i] *APOE* ε4 carrier status includes *APOE* genotypes 2/4, 3/4, and 4/4.

[j] Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet scores range from 0 to 14, with higher scores reflecting higher adherence and degree to which epidemiological evidence indicates greater brain health in older adults.

[k] The Modified Telephone Interview for Cognitive Status (TICSm) (unadjusted scores) is a test of global cognitive function ranging from 0 to 50, with higher scores reflecting better performance.

[l] Mini-Mental State Examination (MMSE) scores range from 0 to 30, with higher scores reflecting higher overall cognitive function.

[m] The Geriatric Depression Scale is a self-administered questionnaire ranging from 0 to 15, with higher scores reflecting worse mood.

[n] Cognitive status at baseline was adjudicated to identify mild cognitive impairment or dementia by an expert panel using all cognitive, medical, and self-reported data.

subgroup analyses examined consistency of the intervention effect on the primary outcome by baseline cognitive function (median split of global cognitive composite score) and *APOE* ε4 carrier status (yes or no). Exploratory subgroup analyses were also examined by sex (female or male), age (<70 or ≥70 years), and baseline cardiometabolic health (Framingham risk: low [<10%], medium [10%-20%], or high [>20%][30]; or prevalent cardiovascular disease: self-reported myocardial infarction, cardiac arrest, congestive heart failure, uncontrolled arrhythmia, uncontrolled angina, stent placement, angioplasty, coronary artery bypass graft surgery, valve replacement, deep vein thrombosis or pulmonary embolism, stroke, or transient ischemic attack). Results of subgroup analyses are reported with 95% confidence intervals and nominal *P* values.

Adverse event rates were compared using Poisson regression.

Analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Figure 2 shows participant flow through the trial. Of 13 285 individuals who initiated screening, 2111 were randomized to the structured (n = 1056) or self-guided (n = 1055) interventions (see eTable 3 in Supplement 3 for allocation by clinical site) from May 2019 to March 2023. Most exclusions were

Table 2. Cognitive Outcomes Based on Mixed-Effects Models for Repeated Measures Comparing Annual Rate of Change (Slope) Between Intervention Groups, With Covariate Adjustment

Outcomes	Mean rate of change per year, SD (95% CI)		Mean between-group difference in rate of change per year (95% CI)[a]	*P* value
	Structured	Self-guided		
Global cognitive function composite (primary outcome)	0.243 (0.227-0.258)	0.213 (0.198-0.229)	0.029 (0.008 to 0.050)	.008
Individual components of the global cognitive function composite outcome				
Executive function	0.160 (0.140-0.180)	0.122 (0.102-0.141)	0.037 (0.010 to 0.064)	
Episodic memory	0.250 (0.230-0.270)	0.239 (0.219-0.259)	0.009 (−0.019 to 0.037)	
Processing speed	0.178 (0.158-0.198)	0.155 (0.136-0.175)	0.023 (−0.004 to 0.050)	

[a] Adjusted for site (stratification factor), baseline age, test version (if >1 version used), number of prior assessments (to control for practice effects), and number of prior assessments × age interaction.

due to high MIND diet score, not being sedentary, low cognitive function, age, or not meeting other prespecified risk criteria. Despite a pause on in-person visits from March to July 2020 due to COVID-19, enrollment remained on track (eFigure 1 in Supplement 3). Overall, 43 structured and 39 self-guided participants discontinued the intervention. The last participant exited on May 14, 2025. A total of 1941 participants (92%) completed month 6 clinic assessments, 1898 (90%) completed month 12 assessments, 1847 (87%) completed month 18 assessments, and 1879 (89%) completed month 24 assessments.

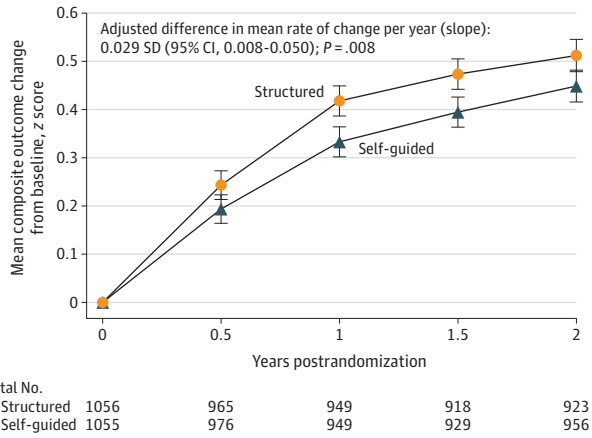
Both intervention groups were similar in demographics and risk factors for cognitive decline (**Table 1**). Overall, the cohort was largely cognitively healthy, with a median Mini-Mental State Examination score of 29 (IQR, 28-30), and less than 5% of participants had mild cognitive impairment adjudicated at baseline. The mean age was 68.2 (SD, 5.2) years, 68.9% were female, 30.8% represented racial and ethnic minority groups, 30.0% did not have a college degree, and the mean modified Telephone Interview for Cognitive Status score was 37.6 (SD, 3.3). Baseline cognitive test scores were comparable across groups (eTable 4 in Supplement 3).

Mean intervention adherence measured using team meeting attendance exceeded the 80% goal for both groups, with 91.0% for structured and 94.8% for self-guided (eFigure 2A in Supplement 3). Attendance varied slightly among subgroups (eFigure 2B-H in Supplement 3) but remained high overall.

Global cognitive composite scores increased over time for both groups at a mean rate of 0.243 SD (95% CI, 0.227-0.258) per year for structured and 0.213 SD (95% CI, 0.198-0.229) per year for self-guided after prespecified covariate adjustment. The mean difference in rate of change in these scores between groups—the primary outcome—was 0.029 SD per year (95% CI, 0.008-0.050; $P = .008$) (**Table 2** and **Figure 3**). Changes in unadjusted global composite *z* scores by intervention group are shown in eFigure 3 in Supplement 3. Results of supporting analyses are presented in eAppendix 1 in Supplement 3, which show no evidence that differential missing data and choice of statistical model biased findings.

Analyses of intervention effects on the primary outcome's constituent cognitive domains (prespecified secondary outcomes) showed greater improvement in executive function for the structured group vs the self-guided group

Figure 3. Change From Baseline in Global Cognitive Function Composite Score (Primary Outcome) by Structured vs Self-Guided Lifestyle Interventions



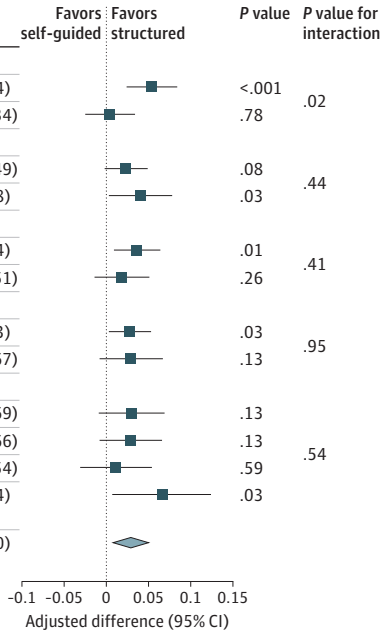
Mean changes from baseline for the global cognitive function composite score fitted using linear contrasts from a mixed-effects model for repeated measures including all available participant data. Global cognitive function composite *z* scores are scaled to have SD = 1, so nearly 70% of participants obtain a score within 1 SD of the mean. Higher values indicate improved performance relative to baseline. Whiskers indicate 95% CIs. Included are results from the per-protocol analysis to compare slopes (SDs per year) between groups after adjustment for clinical site, baseline age, practice effects, and test version. Mean rate of change over time per year (slope): structured group, 0.243 SD (95% CI, 0.227-0.258); self-guided group, 0.213 SD (95% CI, 0.198-0.229). See eFigure 3 in Supplement 3 for raw score box-and-whisker plots of the global and domain-specific composite scores.

by 0.037 SD (95% CI, 0.010-0.064) per year. Processing speed showed a similar pattern, with a difference of 0.023 SD (95% CI, −0.004 to 0.050) per year favoring the structured group, which did not reach statistical significance. Increases in episodic memory did not differ by intervention group at 0.009 SD (95% CI, −0.018 to 0.037) per year. These findings are summarized in Table 2, and unadjusted composite *z* scores by cognitive domain and intervention group are shown in eFigure 3 in Supplement 3.

The structured intervention effect on the primary outcome did not significantly differ by *APOE* ε4 carrier status ($P = .95$ for interaction) but appeared to be more potent for participants with lower baseline cognitive function (lower: 0.054 SD [95% CI, 0.024-0.084]; higher: 0.004 SD [95% CI, −0.025

Figure 4. Intervention Effects on Global Cognitive Function Composite Score (Primary Outcome) by Prespecified Subgroups

Subgroup	Structured		Self-guided		Adjusted difference (95% CI)	P value	P value for interaction
	No. of participants	Mean change per y in SD (95% CI)	No. of participants	Mean change per y in SD (95% CI)			
Baseline cognition							
Less than median	540	0.255 (0.233-0.276)	516	0.202 (0.180-0.224)	0.054 (0.024 to 0.084)	<.001	.02
Median or higher	516	0.231 (0.209-0.253)	539	0.224 (0.203-0.245)	0.004 (-0.025 to 0.034)	.78	
Sex							
Female	721	0.238 (0.219-0.256)	734	0.214 (0.196-0.232)	0.023 (-0.002 to 0.049)	.08	.44
Male	335	0.253 (0.226-0.280)	321	0.212 (0.185-0.239)	0.041 (0.003 to 0.078)	.03	
Age, y							
<70	600	0.275 (0.254-0.295)	608	0.237 (0.217-0.257)	0.036 (0.009 to 0.064)	.01	.41
≥70	456	0.202 (0.179-0.225)	447	0.182 (0.158-0.205)	0.018 (-0.014 to 0.051)	.26	
APOE ε4 carrier							
No	731	0.257 (0.238-0.275)	713	0.229 (0.210-0.247)	0.028 (0.003 to 0.053)	.03	.95
Yes	322	0.212 (0.185-0.240)	338	0.182 (0.155-0.209)	0.029 (-0.008 to 0.067)	.13	
Framingham risk							
Low	289	0.269 (0.240-0.298)	331	0.235 (0.209-0.262)	0.030 (-0.009 to 0.069)	.13	
Medium	344	0.243 (0.216-0.270)	334	0.214 (0.187-0.241)	0.029 (-0.008 to 0.066)	.13	.54
High	261	0.219 (0.189-0.250)	268	0.208 (0.179-0.238)	0.011 (-0.031 to 0.054)	.59	
Prevalent cardiovascular disease	162	0.233 (0.195-0.272)	119	0.161 (0.116-0.206)	0.066 (0.007 to 0.124)	.03	
Overall	1056	0.243 (0.227-0.258)	1055	0.213 (0.198-0.229)	0.029 (0.008 to 0.050)		



Changes per year in adjusted global cognitive composite *z* scores (SDs) for prespecified subgroups by intervention group assignment and differences between groups after adjustment for clinical site, baseline age, practice effects, and test version. The raw *P* values (not adjusted for multiple comparisons) compare changes over time for levels within a subgroup and tests of interaction across subgroup levels by intervention group assignment to assess the consistency of relative intervention effects on the primary outcome.

to 0.034]; *P* = .02 for interaction). Results of exploratory subgroup analyses suggest consistent structured intervention effects by sex (*P* = .44 for interaction), age (*P* = .41 for interaction), and baseline cardiovascular health (*P* = .54 for interaction). These findings are summarized in **Figure 4**.

Fewer ascertained adverse events (collected by unmasked assessors during clinic visits) were reported for the structured group than the self-guided group (eTable 5A in Supplement 3). For serious adverse events, ascertained totals were 151 for structured and 190 for self-guided (difference, *P* = .03). The structured group had 9 serious adverse events judged as intervention related and 11 deaths; the self-guided group had 2 serious adverse events judged as intervention related and 5 deaths. For nonserious adverse events, ascertained totals were 1091 for structured and 1225 for self-guided (difference, *P* = .005). Volunteered nonserious adverse events were more common in the structured group (685 vs 140 in self-guided group), likely reflecting more frequent staff contact and thus more reporting opportunity. The most common *MedDRA* codes for serious adverse events and adverse events (eTable 5B-C in Supplement 3) showed low overall rates with some group differences: more infections, neoplasms, and kidney disorders in the structured group; more nervous system disorders in the self-guided group. A positive COVID-19 test result was the most common adverse event (669 [21.3%] of 3141 adverse events reported overall) and was more often reported in the structured group (380 events vs 289 events reported in the self-guided group), although no clustering related to team meetings was observed.

Discussion

The US POINTER trial yielded 3 principal findings. First, in a large cohort of older adults at elevated risk of cognitive decline associated with dementia, multidomain lifestyle interventions were delivered safely and with high adherence. Second, greater structure, accountability, and intervention intensity produced a statistically significant relative enhancement in cognitive benefit over 2 years. Third, this benefit was consistent across several key subgroups.

Both intervention groups showed cognitive improvement over 2 years; however, the structured intervention yielded greater benefit than the self-guided intervention. The upward cognitive trajectories in both groups showing improvement likely reflect, in part, practice effects—commonly observed in studies with repeat assessments,[31] particularly at the second testing.[32] Analyses were adjusted for number of prior assessments to help mitigate this influence.

Assessing clinical significance is challenging given the improvement observed in both groups and the potential influence of practice effects. The additional benefit of 0.029 SD per year for the structured intervention closely aligns with the protocol target of 0.030 SD per year, which was based on the effect size reported in the FINGER trial that also demonstrated reduced decline in activities of daily living[31] (preserved independence) and lower incidence of chronic disease[33] (preserved health) with a similar multidomain intervention. Future analyses of POINTER data, including additional cognitive

measures, functional outcomes, fluid and imaging biomarkers, and longer-term cognitive trajectories, may help clarify the clinical significance and durability of these findings.

These results also raise considerations for public health implementation. Notably, the self-guided group improved despite lower resource demands and participant burden. However, the absence of a no-intervention control limits our ability to rule out alternative explanations for cognitive improvement at this time, including practice effects and general benefits of trial participation. Planned analyses from the extended 4-year follow-up and biomarker substudies[22] will provide further insight into long-term impact and comparative effectiveness across groups.

The global cognitive composite was calculated as the mean of composite *z* scores for executive function, episodic memory, and processing speed. To provide context for interpreting the primary outcome, we examined domain composite trajectories across groups. These analyses indicated that executive function and processing speed were the primary contributors to the overall effect, whereas change in episodic memory did not differ between groups—a pattern also observed in the FINGER trial.[8] Executive function may be especially responsive to behaviors that reduce cardiometabolic risk. Aerobic exercise is associated with improvements in executive function[34] and increased prefrontal gray matter volume,[35] while a Mediterranean diet may further enhance executive function via cardiovascular benefits.[36] Cognitive benefits did not differ between *APOE* ε4 carriers and noncarriers, suggesting that lifestyle interventions may be effective even among individuals at elevated cardiovascular or genetic risk of dementia. Future analyses of expanded domain composites that incorporate additional measures may further clarify domain-specific contributions to the primary outcome.

This trial enrolled older adults at increased risk of cognitive decline due to sedentary behavior, suboptimal diet, family history of memory loss, and cardiometabolic risk factors. Participants were recruited from 5 different geographical US regions and represented diverse ethnoracial backgrounds. National data indicate that up to 35% of older adults do not meet physical activity guidelines,[37] 81% consume suboptimal diets,[38] and nearly 55% meet criteria for metabolic syndrome (≥3 risks).[39] These estimates highlight the prevalence of eligibility-targeted characteristics and support generalizability to the broader US population. Subgroup analyses (Figure 4) showed consistent benefits of the structured intervention over the self-guided intervention across *APOE* ε4 carrier status, sex, age, and cardiometabolic health, reinforcing applicability to a heterogeneous at-risk population. The possibility of greater structured intervention benefit among individuals with lower cognitive function is intriguing but warrants further investigation.

Serious adverse events occurred at similar rates: 12% of structured participants and 14% of self-guided participants experienced at least 1 ascertained event. Voluntarily reported serious adverse events were more common in the structured group (n = 91) than in the self-guided group (n = 47), likely reflecting more contact with study staff. In contrast, ascertained serious adverse events, collected during 6-month clinic visits, were less frequent for the structured group (n = 151) than for the self-guided group (n = 190). The structured group experienced more gastrointestinal disorders and infections; gastrointestinal symptoms may be related to dietary changes, although the higher rate of infections is unexplained. There were no notable group differences in ascertained serious adverse events related to musculoskeletal issues or fractures.

The structured intervention was considered higher intensity due to the frequency of team meetings (38 vs 6 in the self-guided group over 2 years) and the regular, intentional engagement expected for adherence to intervention activities. Participants were encouraged to practice healthy behaviors weekly to support long-term, sustainable change. Key components for implementation included regular facilitated team meetings and access to community-based resources (eg, exercise facilities), both of which could be feasibly delivered in real-world settings to support widespread health behavior change.

Strengths of this trial include its randomized design, recruitment of a diverse cohort, high retention, rigorous masking, standardized implementation, and strong intervention fidelity and adherence.

Limitations

This study has several limitations. First, generalizability may be limited by inclusion of only 5 sites, by selective enrollment criteria to enrich risk of cognitive decline, and by the requirement to be randomized and complete a 2-year trial with extensive phenotyping. Second, the trial was not powered to assess cognitive impairment or dementia outcomes. Third, the self-guided group did not serve as a true no-intervention control. Fourth, participants were unmasked to intervention assignment. Fifth, the durability, scalability, and long-term clinical significance of the intervention remain unknown. Sixth, although there is no evidence that missing data biased the findings, this possibility cannot be completely ruled out.

Conclusions

US POINTER demonstrated that multidomain lifestyle interventions can be safely and effectively delivered to older adults. Although global cognitive function improved for both intervention groups, greater benefit was observed with the structured multidomain intervention, which promoted regular physical exercise, adherence to the MIND diet, cognitive and social challenge, and health monitoring. Further research is needed to understand the clinical significance of this difference and assess longer-term clinical outcomes of both interventions.

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