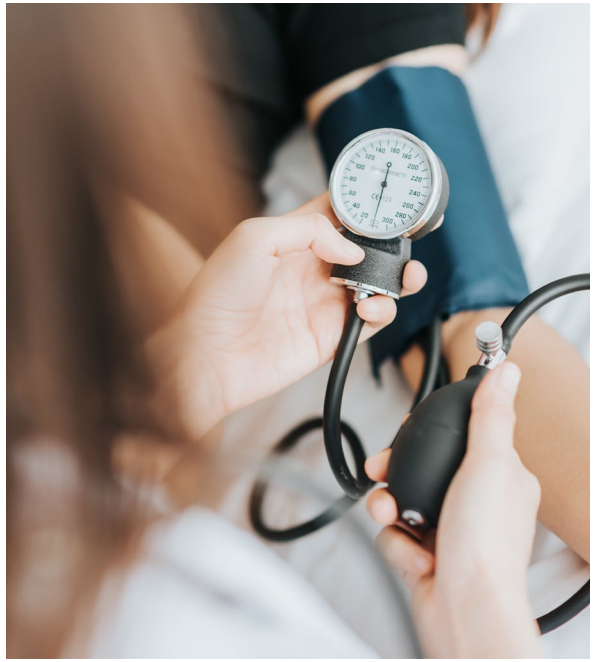
U.S. POINTER

Topline Results of a Large Multisite Randomized Controlled Multidomain Lifestyle Intervention Trial



Tina Brinkley, PhD

on behalf of the U.S. POINTER Leadership & Study Group

DISCLOSURES

Funding

Alzheimer's Association
U.S. POINTER main trial

NIH/National Institute on Aging
POINTER Neuroimaging ancillary study
POINTER-zzz Sleep ancillary study
POINTER-Neurovascular ancillary study
POINTER-Microbiome ancillary study

Overview of U.S. POINTER

Primary Objective

Compare the effects of two multidomain lifestyle interventions on global cognitive function in 2000 older adults at risk for cognitive decline and dementia

Study Design, Participants & Interventions

2-year RCT; enrolled diverse cohort of 2,111 cognitively healthy older adults at risk for cognitive decline due to lifestyle, health, and demographic factors; clinic assessments at baseline and every 6 months; randomized to one of two interventions

STR — 38 peer team meetings over 2 years with study Navigator and Interventionist for goal-setting, accountability and support

- **Physical Exercise**: Aerobic, resistance, and stretching & balance exercise
- **Nutrition**: MIND diet
- **Cognitive and Social Challenge**: Computer cognitive training and participation in other challenging social & intellectual activities
- **Guideline-Based Health Coaching**

SG — 6 peer team meetings over 2 years with study Navigator

- **Education & General Support**
  - Health education
  - Tools to support self-guided plans
  - General encouragement
- **Health Monitoring**

Executive Function

- Number Span Backward
- Number Sequencing (alphanumeric sequencing)
- Word Fluency (letter, category)
- Trails B (time)

Primary Outcome:

Global Cognitive Composite

Constructed from equally weighted cognitive domain composites

Processing Speed

- Trails A (time)
- Digit Symbol Substitution Test

Memory

- Free & Cued Selective Reminding Test (immediate & delayed recall)
- Story Recall (immediate, delayed)
- Visual Paired Associates (immediate, delayed recall)

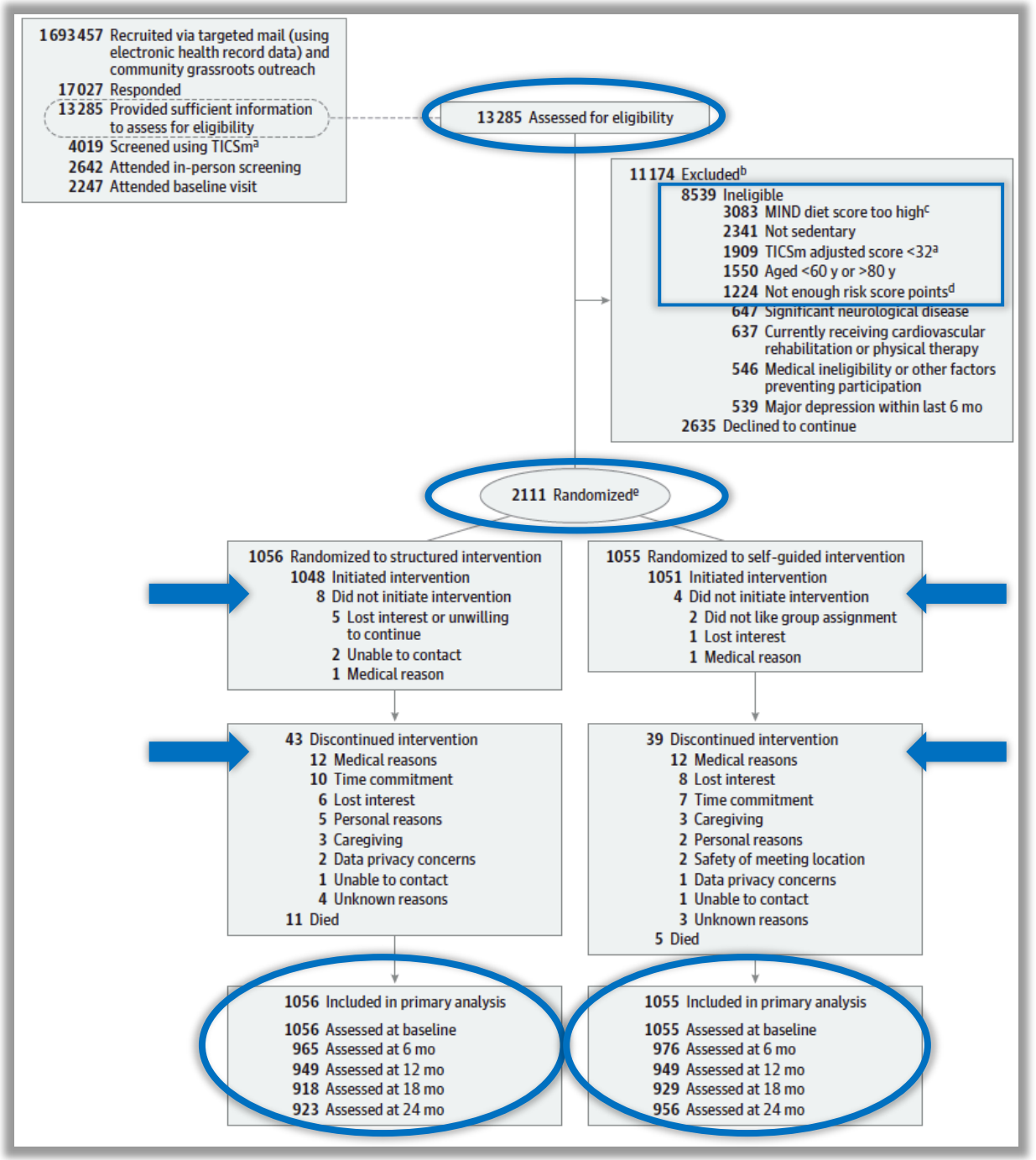
Individual test scores converted to z-scores using the baseline mean and SD

Composite score: mean of individual test z-scores, renormalized to SD of 1 at baseline

Primary Analysis – Statistical Model

- Intent to treat: all data from all participants analyzed according to group assignment
- Mixed-effects model for repeated measures, using restricted maximum likelihood with an unstructured covariance
- Independent variables: participant, intervention assignment, time (continuous by assessment visit: 0, 0.5, 1.0, 1.5, 2.0 years)
- Covariates: site (stratification factor), baseline age, test version (if >1 version used), number of prior assessments (to control for practice effects), prior assessments x age
- Two-tailed type 1 error: 0.05
- Intervention x time tested whether covariate-adjusted slopes differed between groups
- Missing data assumed missing at random; inverse probability weighting used to assess impact of missing data

CONSORT


1 693 457 Recruited via targeted mail (using electronic health record data) and community grassroots outreach
17 027 Responded
13 285 Provided sufficient information to assess for eligibility
4019 Screened using TICSm[a]
2642 Attended in-person screening
2247 Attended baseline visit
13 285 Assessed for eligibility
11 174 Excluded[b]
8539 Ineligible
3083 MIND diet score too high[c]
2341 Not sedentary
1909 TICSm adjusted score <32[a]
1550 Aged <60 y or >80 y
1224 Not enough risk score points[d]
647 Significant neurological disease
637 Currently receiving cardiovascular rehabilitation or physical therapy
546 Medical ineligibility or other factors preventing participation
539 Major depression within last 6 mo
2635 Declined to continue
2111 Randomized[e]
1056 Randomized to structured intervention
1048 Initiated intervention
8 Did not initiate intervention
5 Lost interest or unwilling to continue
2 Unable to contact
1 Medical reason
1055 Randomized to self-guided intervention
1051 Initiated intervention
4 Did not initiate intervention
2 Did not like group assignment
1 Lost interest
1 Medical reason
43 Discontinued intervention
12 Medical reasons
10 Time commitment
6 Lost interest
5 Personal reasons
3 Caregiving
2 Data privacy concerns
1 Unable to contact
4 Unknown reasons
11 Died
39 Discontinued intervention
12 Medical reasons
8 Lost interest
7 Time commitment
3 Caregiving
2 Personal reasons
2 Safety of meeting location
1 Data privacy concerns
1 Unable to contact
3 Unknown reasons
5 Died
1056 Included in primary analysis
1056 Assessed at baseline
965 Assessed at 6 mo
949 Assessed at 12 mo
918 Assessed at 18 mo
923 Assessed at 24 mo
1055 Included in primary analysis
1055 Assessed at baseline
976 Assessed at 6 mo
949 Assessed at 12 mo
929 Assessed at 18 mo
956 Assessed at 24 mo

Primary Outcome: Global Cognitive Composite

mean rate of change per year (slope)

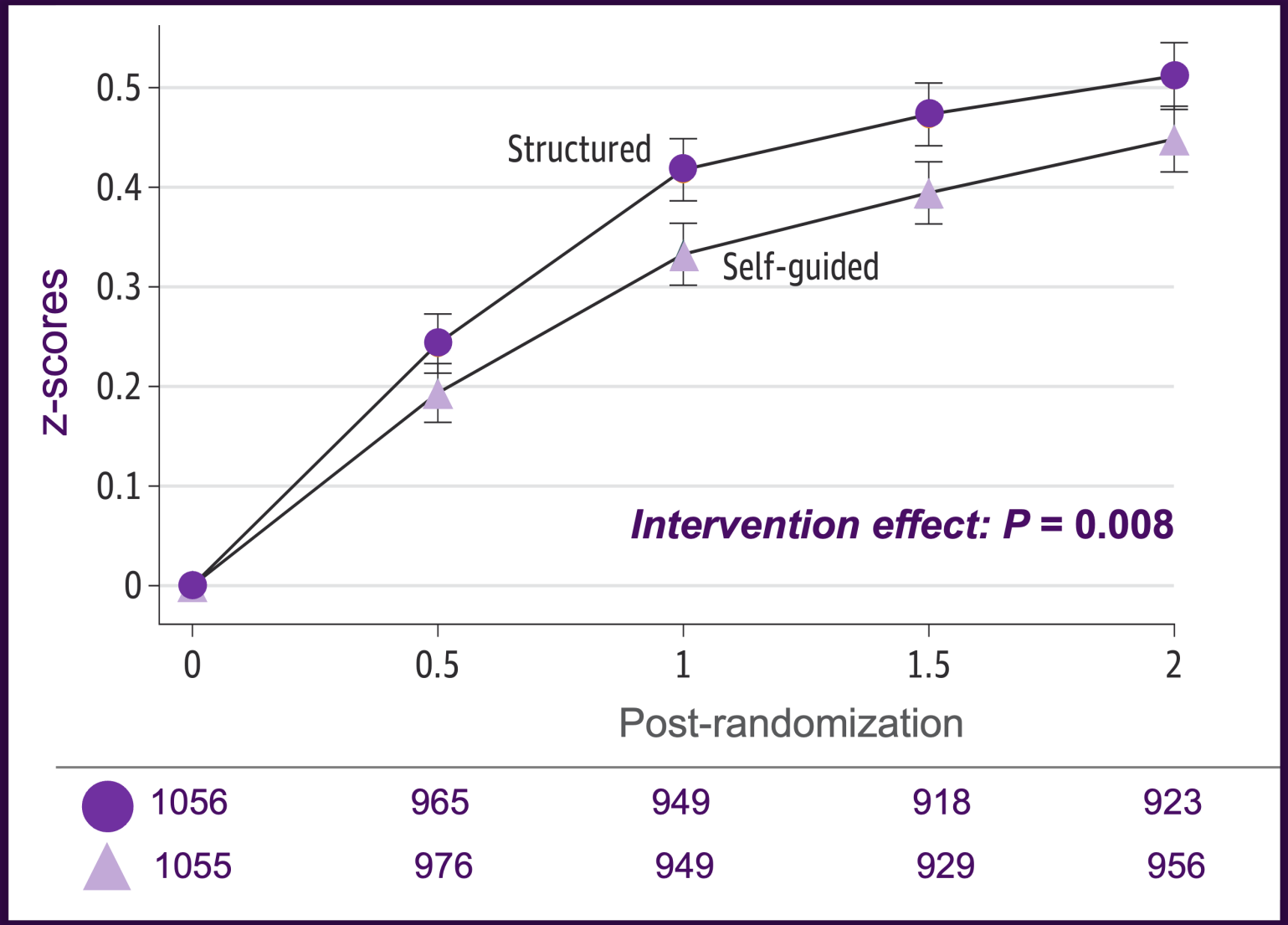
Structured: 0.243 SD per year (95% CI, 0.227 - 0.258)

Self-Guided: 0.213 SD per year (95% CI, 0.198 - 0.229)

Adjusted group difference

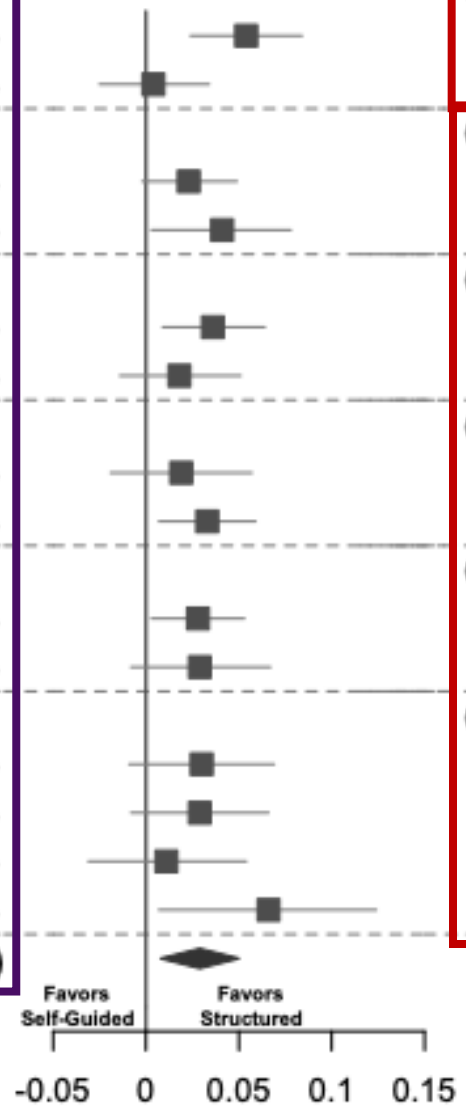
0.029 SD per year (95% CI, 0.008 - 0.050)

Post-hoc analyses evaluated sensitivity of results to model assumptions; slope-based model was more conservative relative to other models tested (e.g., area between the curves, *P = 0.0002*)



Consistency of Primary Outcome Across Key Subgroups

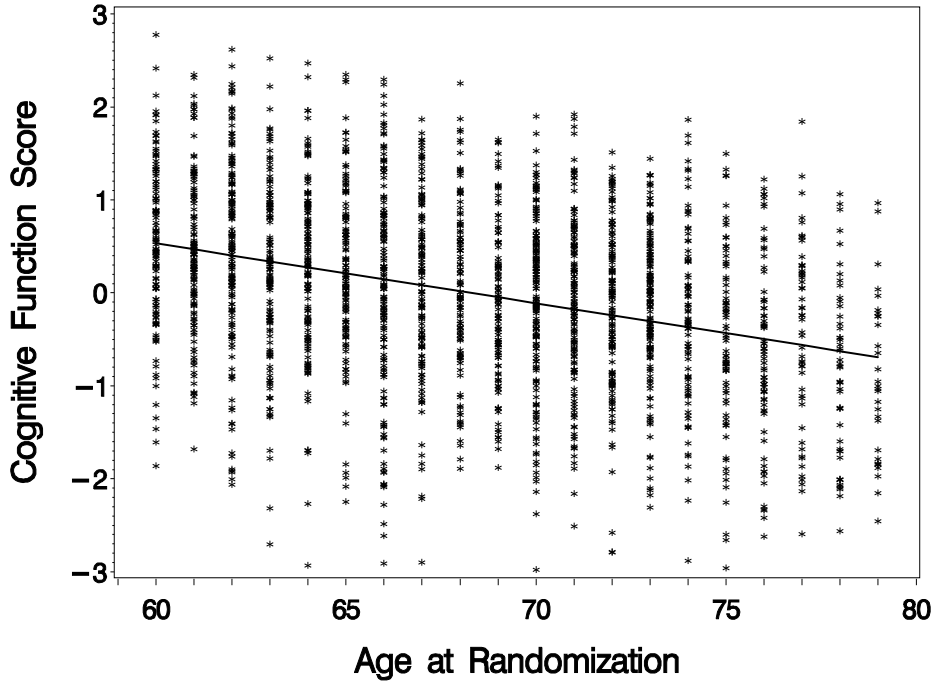
	Structured Mean Change per Year (95% CI), N	Self-Guided Mean Change per Year (95% CI), N	Adjusted Difference (95% CI)	p-value for Interaction
Baseline Cognition				0.02
< Median	0.255 (0.233, 0.276), 540	0.202 (0.180, 0.224), 515	0.054 (0.024, 0.084)	
≥ Median	0.231 (0.209, 0.253), 516	0.224 (0.203, 0.245), 540	0.004 (-0.025, 0.034)	
Sex				0.44
Female	0.238 (0.219, 0.256), 721	0.214 (0.196, 0.232), 734	0.023 (-0.002, 0.049)	
Male	0.253 (0.226, 0.280), 335	0.212 (0.185, 0.239), 321	0.041 (0.003, 0.078)	
Age				0.41
< 70 years	0.275 (0.254, 0.295), 600	0.237 (0.217, 0.257), 608	0.036 (0.009, 0.064)	
≥ 70 Years	0.202 (0.179, 0.225), 456	0.182 (0.158, 0.205), 447	0.018 (-0.014, 0.051)	
Ethnoracial Identification				0.62
Minority	0.241 (0.214, 0.269), 326	0.223 (0.195, 0.250), 321	0.019 (-0.019, 0.057)	
Not Minority	0.243 (0.224, 0.261), 725	0.210 (0.192, 0.228), 729	0.033 (0.007, 0.059)	
APOE ε4 Carrier				0.95
No	0.257 (0.238, 0.275), 731	0.229 (0.210, 0.247), 713	0.028 (0.003, 0.053)	
Yes	0.212 (0.185, 0.240), 322	0.182 (0.155, 0.209), 338	0.029 (-0.008, 0.067)	
FRS				0.54
Low	0.269 (0.240, 0.298), 289	0.235 (0.209, 0.262), 331	0.030 (-0.009, 0.069)	
Medium	0.243 (0.216, 0.270), 344	0.214 (0.187, 0.241), 334	0.029 (-0.008, 0.066)	
High	0.219 (0.189, 0.250), 261	0.208 (0.179, 0.238), 268	0.011, (-0.031, 0.054)	
Prevalent CVD	0.233 (0.195, 0.272), 162	0.161 (0.116, 0.206), 119	0.066 (0.007, 0.124)	
OVERALL	**0.243 (0.227, 0.258), 1056**	**0.213 (0.198, 0.229), 1055**	**0.029 (0.008, 0.050)**	

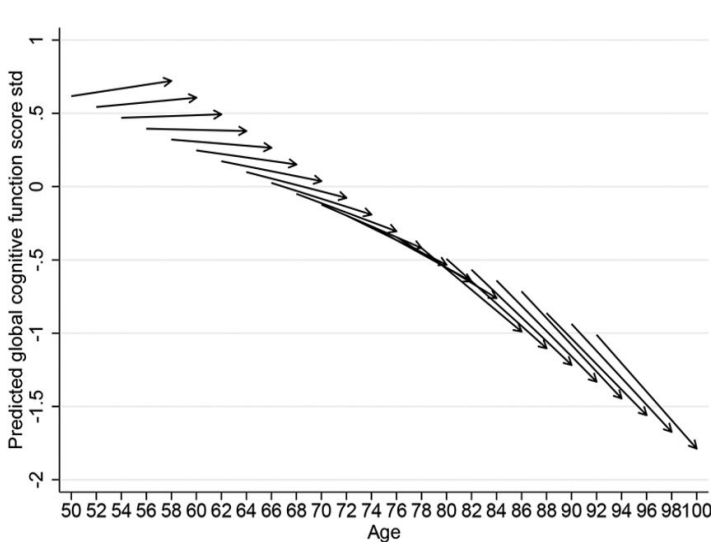


Favors Self-Guided Favors Structured

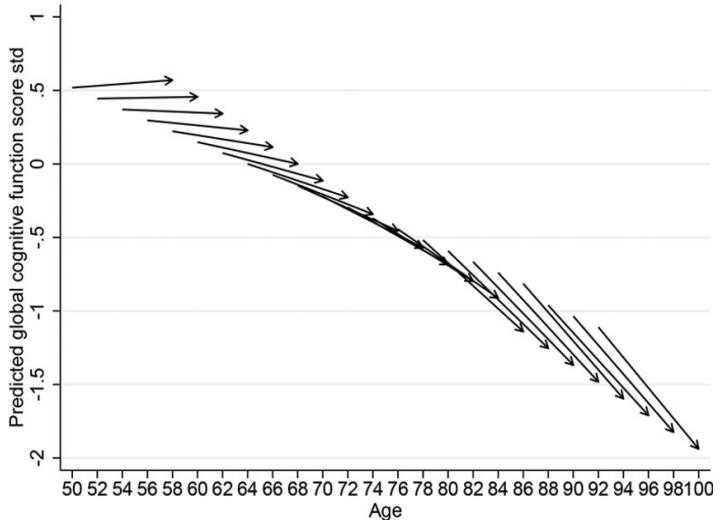
Assessing Clinical Relevance

How does global cognitive function decline with age when there is no lifestyle intervention?





Females



Males

U.S. POINTER at Baseline: -0.064 SD per year (cross-sectional)

English Longitudinal Study of Aging: -0.037 SD per year

Paola Zaninotto et al. J Epidemiol Community Health 2018;72:685-694

Assessing Clinical Relevance

Extra Cognitive Benefit of the Structured Intervention?

- Based on modeling of expected annual aging-related cognitive decline, we estimate that – relative to the Self-guided group – participants in the Structured group performed at a level comparable to adults 1 to 2 years younger in age.
- A 2-year lifestyle intervention that slows or offsets decline by 1 to 2 years may have a meaningful downstream impact on multiple levels.

Other Data to Address Relevance & Durability of Intervention Effects

- *Cogstate subtests and Digital Clock Test to expand domain composites*
- *Cogstate C3 battery*
- *BrainHQ Assessment*
- *Clinical Dementia Rating Scale*
- *Instrumental Activities of Daily Living*
- *Everyday Cognition Scales*
- *Cognitive Change Index*
- *Frailty Index*

- *Blood biomarkers*

- *Adjudicated cognitive status (MCI, dementia) at baseline and follow-up*

- *Ongoing 4-year extended follow-up (no intervention) with annual assessments*

U.S.POINTER ALZHEIMER'S ASSOCIATION

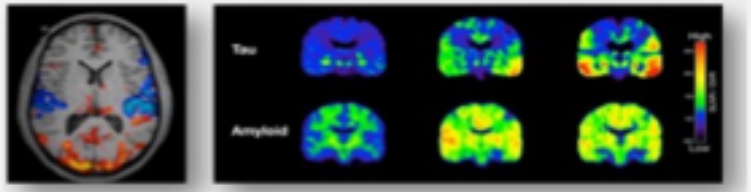
NIA-Funded Ancillary Studies

N=1052 (32% URG; >30% Aβ+)

Neuroimaging Ancillary (MRI, amyloid/tau PET)

PI: Susan Landau (Berkeley)

NIH/NIA R01 AG062689

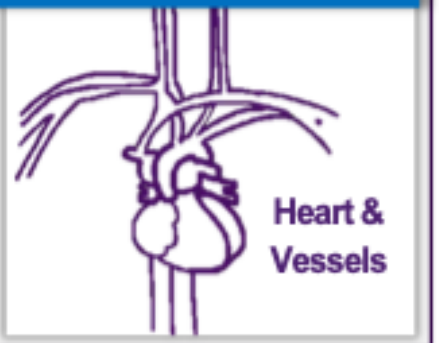


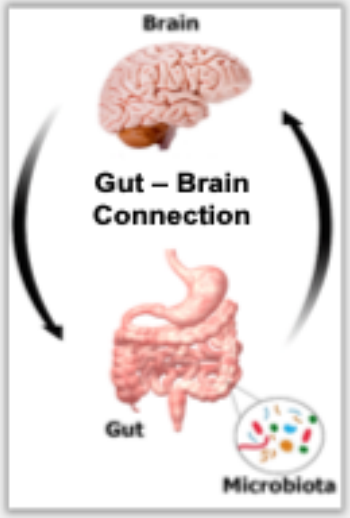
N=480 (32% URG; 50% w/accelerated vessel aging)

Neurovascular Ancillary (Ultrasound, Tonometry)

PIs: Tina Brinkley & Hossam Shaltout (Wake Forest)

NIH/NIA R01 AG066910





N=807 (34% URG)

Gut Microbiome Ancillary (Metagenomic & Metabolomic Profiling)

PIs: Rima Kaddurah-Daouk (Duke), Ali Keshavarzian (Rush)

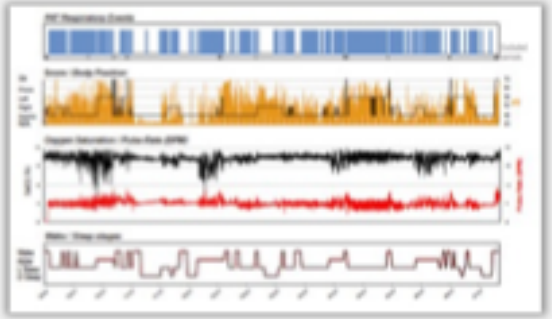
NIH/NIA U19 AG063744

POINTER Sleep Ancillary (Oximetry, Actigraphy)

PIs: Kate Hayden & Laura Baker (Wake Forest)

NIH/NIA R01 AG064440

N=780 (34% URG; 63% with sleep apnea)



Intervention Results to be reported at CTAD, December 3, 2025, San Diego, CA

71 countries (90 teams) participating, planning or have completed multi-domain non-pharmacological risk modification intervention trials → 20,000+ participants

Kivipelto, Mangialasche et al. World-Wide FINGERS Network: A Global Approach to Risk Reduction and Prevention of Dementia *(Alzheimer's Dement, July 6, 2020)*

U.S. POINTER: Public Health Implications

Generalizability of POINTER

68 years old, 68% female 31% from ethnoracial minorized groups, 30% without a college degree, CVD metrics are borderline high, 79% have family history of memory loss, 30% ApoE4 carriers

In the US: at least 35% of older adults do not meet physical activity guidelines, 81% consume suboptimal diets, and 55% meet criteria for metabolic syndrome (≥3 CVD risks).

→ Highlight prevalence of eligibility-targeted characteristics in the U.S. population.

Feasibility of POINTER Interventions

- Intervention delivered in the community
- Access to trained and experienced personnel for guidance and support
- Access to peer support groups
- Access to resources to support behavior change
- **Implications for cost-effectiveness, feasibility, and sustainability**

Summary & Conclusions

- **Cohort:** We successfully recruited and enrolled a diverse and largely representative older adult population enriched for risk of cognitive decline – and with room intervention-related improvement

- **Interventions:** Our interventions were adopted and sustained by participants, and successfully delivered using community partners and resources – provides solid foundation for feasibility, sustainability, and therefore → implementation

- **Results:** Both intervention groups improved, but the Structured intervention led to a significantly greater benefit. This extra benefit for the Structured group was consistent across several key subgroups.

- **Next Steps:** Extensive biomarker and ancillary study data still to be examined. Ongoing 4-year observational extension allows assessment of durability of intervention effects. Work beginning to implement into clinical care.

JAMA

Baker LD, Espeland MA, Whitmer RA, et al

Structured vs Self-Guided Multidomain Lifestyle Interventions for Global Cognitive Function

The US POINTER Randomized Clinical Trial

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Alzheimer's Association International Conference

Available at jama.com

Scan to read the article

Acknowledgements.... Study Leadership

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