Risk Reduction Through Non-Pharmacological Intervention

Laura Baker, PhD
Professor of Internal Medicine, Neurology, & Public Health Sciences
Associate Director, Wake Forest Alzheimer's Disease Research Center

Wake Forest University
School of Medicine

1

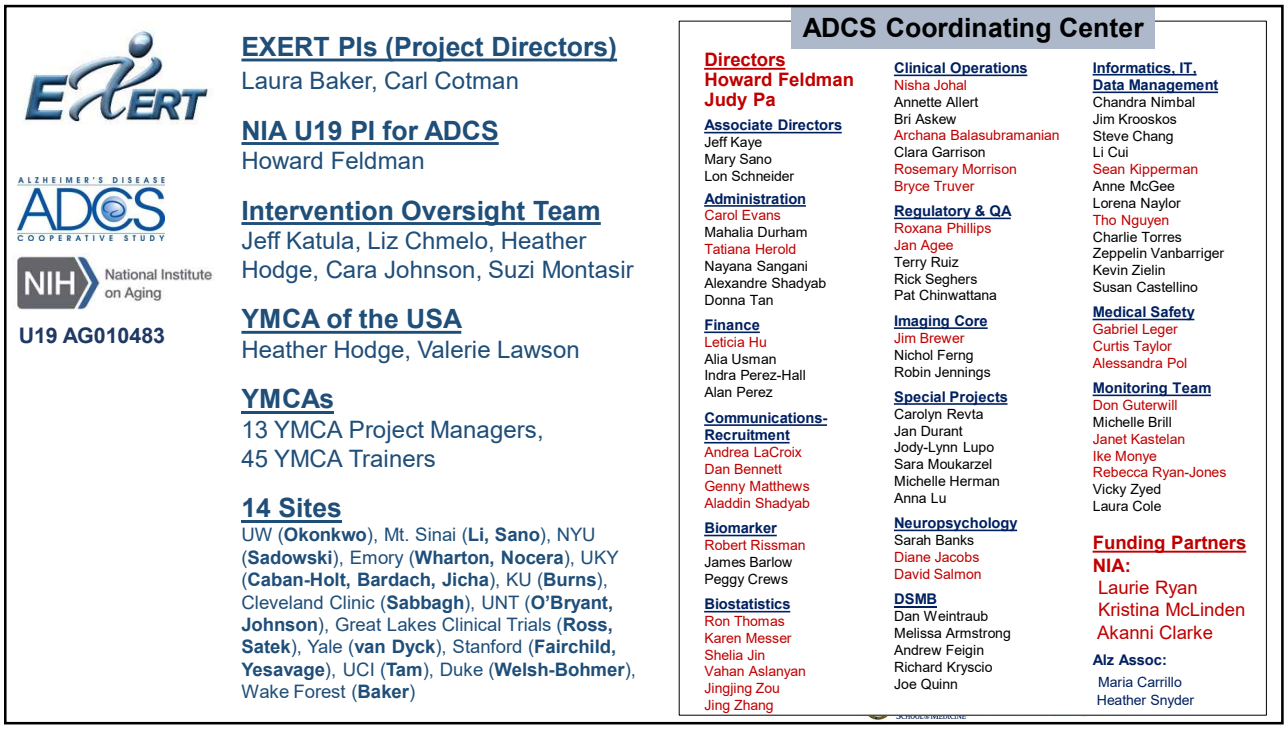
Disclosures

Funding:

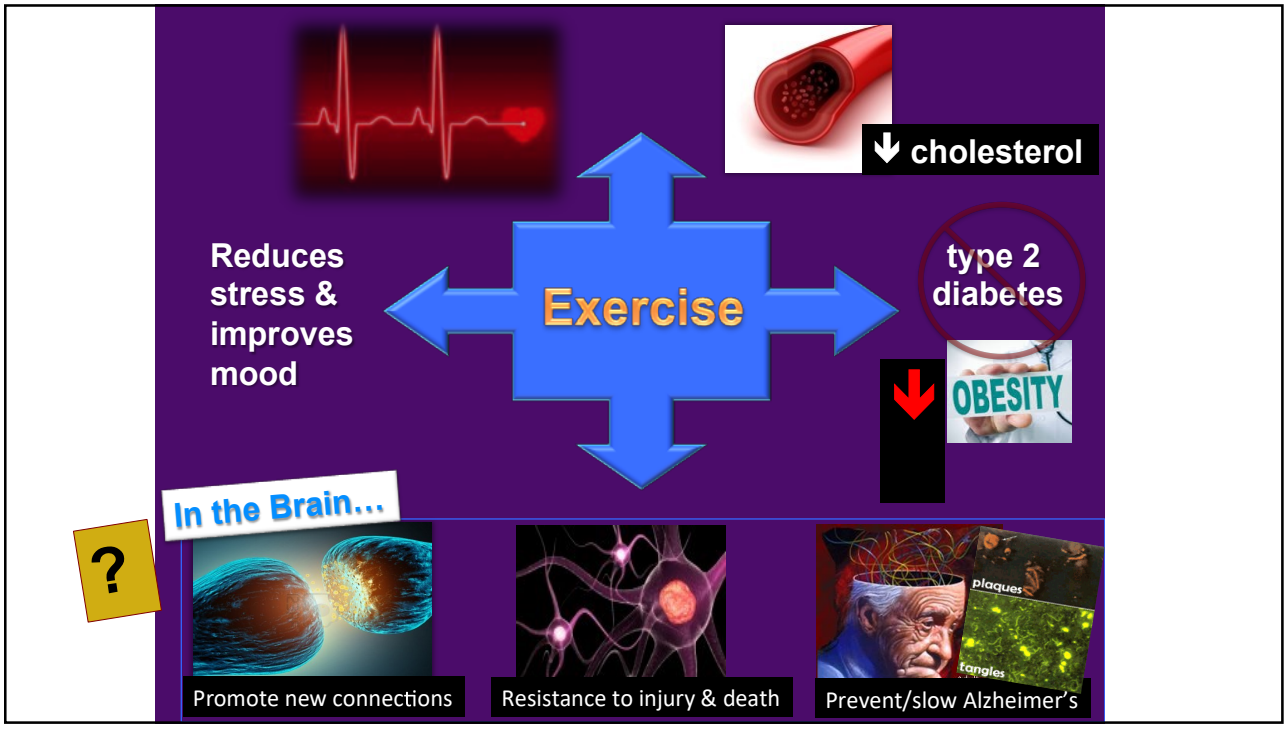
EXERT: NIH National Institute on Aging; ADCS Alzheimer's Disease Cooperative Study

U.S. POINTER: Alzheimer's Association

2


EXERT PIs (Project Directors)
Laura Baker, Carl Cotman
NIA U19 PI for ADCS
Howard Feldman
Intervention Oversight Team
Jeff Katula, Liz Chmelo, Heather Hodge, Cara Johnson, Suzi Montasir
YMCA of the USA
Heather Hodge, Valerie Lawson
YMCAs
13 YMCA Project Managers, 45 YMCA Trainers
14 Sites
UW (Okonkwo), Mt. Sinai (Li, Sano), NYU (Sadowski), Emory (Wharton, Nocera), UKY (Caban-Holt, Bardach, Jicha), KU (Burns), Cleveland Clinic (Sabbagh), UNT (O'Bryant, Johnson), Great Lakes Clinical Trials (Ross, Satek), Yale (van Dyck), Stanford (Fairchild, Yesavage), UCI (Tam), Duke (Welsh-Bohmer), Wake Forest (Baker)
U19 AG010483
ADCS Coordinating Center
Directors
Howard Feldman
Judy Pa
Associate Directors
Jeff Kaye
Mary Sano
Lon Schneider
Administration
Carol Evans
Mahalia Durham
Tatiana Herold
Nayana Sangani
Alexandre Shadyab
Donna Tan
Finance
Leticia Hu
Alia Usman
Indra Perez-Hall
Alan Perez
Communications-Recruitment
Andrea LaCroix
Dan Bennett
Genny Matthews
Aladdin Shadyab
Biomarker
Robert Rissman
James Barlow
Peggy Crews
Biostatistics
Ron Thomas
Karen Messer
Shelia Jin
Vahan Aslanyan
Jingjing Zou
Jing Zhang
Clinical Operations
Nisha Johal
Annette Allert
Bri Askew
Archana Balasubramanian
Clara Garrison
Rosemary Morrison
Bryce Truver
Regulatory & QA
Roxana Phillips
Jan Agee
Terry Ruiz
Rick Seghers
Pat Chinwattana
Imaging Core
Jim Brewer
Nichol Ferng
Robin Jennings
Special Projects
Carolyn Revta
Jan Durant
Jody-Lynn Lupo
Sara Moukarzel
Michelle Herman
Anna Lu
Neuropsychology
Sarah Banks
Diane Jacobs
David Salmon
DSMB
Dan Weintraub
Melissa Armstrong
Andrew Feigin
Richard Kryscio
Joe Quinn
Informatics, IT, Data Management
Chandra Nimbal
Jim Krooskos
Steve Chang
Li Cui
Sean Kipperman
Anne McGee
Lorena Naylor
Tho Nguyen
Charlie Torres
Zeppelin Vanbarriger
Kevin Zielin
Susan Castellino
Medical Safety
Gabriel Leger
Curtis Taylor
Alessandra Pol
Monitoring Team
Don Guterwill
Michelle Brill
Janet Kastelan
Ike Monye
Rebecca Ryan-Jones
Vicky Zyed
Laura Cole
Funding Partners
NIA:
Laurie Ryan
Kristina McLinden
Akanni Clarke
Alz Assoc:
Maria Carrillo
Heather Snyder

3


cholesterol
Reduces stress & improves mood
Exercise
type 2 diabetes
OBESITY
In the Brain…
?
plaques
tangles
Promote new connections
Resistance to injury & death
Prevent/slow Alzheimer's

4

Overview

- Preliminary findings from small or short-duration RCTs that regular physical exercise has potential to slow cognitive decline in adults at increased risk for AD [Lautenschlager 2008, Baker 2010, Nuzum 2020, Biazus-Sehn 2020]
- Phase 3 multi-site randomized clinical trial in 296 older adults with MCI, coordinated through the Alzheimer's Disease Cooperative Study (ADCS) in partnership with Wake Forest University School of Medicine
- Tested the effects of physical exercise on cognitive function using a global composite: ADAS-Cog-Exe


RESEARCH ARTICLE

Development of a novel cognitive composite outcome to assess therapeutic effects of exercise in the EXERT trial for adults with MCI: The ADAS-Cog-Exec

Diane M. Jacobs | Ronald G. Thomas | David P. Salmon | Shelia Jin | Howard H. Feldman | Carl W. Cotman | Laura D. Baker | for the Alzheimer's Disease Cooperative Study EXERT Study Group | for the Alzheimer's Disease Neuroimaging Initiative

ADAS-Cog-Exec

- **ADAS-Cog13 Subtests**: Immediate & Delayed Word Recall, Orientation, Number Cancellation
- **Executive Function**: Trails A & B, Digit Symbol, Category Fluency
- **CDR Box Scores**: Memory, Orientation, Judgement & Problem Solving

5

Aims

Primary

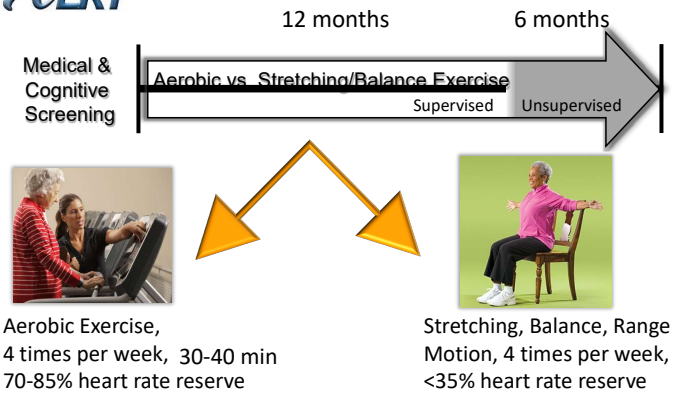
Test whether 12 months of supervised moderate-high intensity aerobic exercise (AX) relative to stretching/balance/range of motion (SBR) can improve or protect cognition measured using ADAS-Cog-Exec in adults with amnestic MCI.

Secondary & Exploratory

- Test intervention effects on:
  - * Executive function and episodic memory composite scores
  - * CDR-SB
  - MRI and ASL brain imaging (hippocampal, prefrontal, AD signature regions)
  - AD blood biomarker (ab42/ab40)
- * Examine intervention effects relative to usual care (no intervention) with modeling using ADNI

6

Study Design



Aerobic Exercise,
4 times per week, 30-40 min
70-85% heart rate reserve

Stretching, Balance, Range of Motion, 4 times per week, 30-40 min
<35% heart rate reserve

- **Outcomes assessments every 6 months**
- **Blood collection every 6 months**
- **Brain imaging at Baseline & Month 12**
- **CSF collection at Baseline & Month 12**

Intervention Oversight

- Supervision by YMCA Trainers
- Central oversight by exercise experts
- Regular Central review of recorded exercise adherence metrics (frequency, duration, intensity)

7

Populations of Interest

Primary: Modified Intent-to-Treat (mITT)

Includes all eligible participants who:

- began the exercise intervention
- completed at least 1 post-baseline primary outcome assessment

Others …

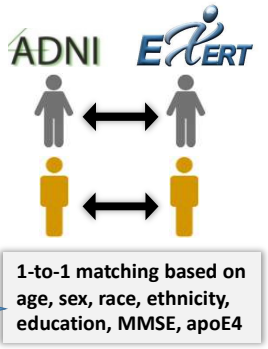
- **Pre-Pandemic** (mITT participants exiting study before pandemic)
- **Per-Protocol** (mITT participants meeting rigorous adherence metrics: attended 70% supervised sessions, mean session duration of 40 min)

8

Analysis Plan

- **Cognition**: tested differences in ADAS-Cog-Exec change scores from baseline to mean of Months 6 & 12, across intervention groups (α=0.05)

- **Usual Care**: compared 12-month changes for each EXERT intervention group relative to matched 'usual care' participants (using ADNI) based on age, sex, ethnicity, education, MMSE, apoE4 (using propensity matching)



9

Amnestic MCI Participants (n=296)

Baseline Characteristics

- Mean (SD) MMSE: 27.9 (1.9)
- Mean (SD) CDR-SB: 1.5 (0.8)
- ApoE4 carrier: 25%

Demographics (n=296)	AX	SBR
Sex (n, % Female)	85 (57.4%)	84 (57.0%)
Race (n, %)		
White	127 (86.4%)	129 (87.2%)
African American	15 (10.2%)	14 (9.5%)
Asian	3 (2.0%)	4 (2.7%)
Native American/Alaskan Native	2 (1.4%)	1 (0.7%)
Ethnicity (n, %)		
Hispanic	3 (2.0%)	0 (0%)
Non-Hispanic	142 (96.0%)	145 (98.0%)
Unknown	3 (2.0%)	3 (2.0%)
Age, years (M, SD)	74.3 (5.7)	74.7 (6.2)
Education, years (M, SD)	16.2 (2.4)	16.3 (2.4)

10

Results: Primary Outcome

No group difference: p=0.29

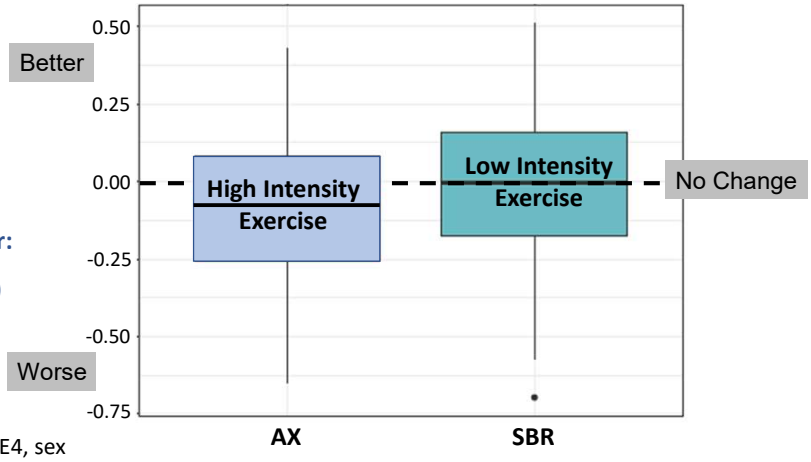
And no decline from baseline at 6 or 12 months for either group …

Same no group difference results for:

- Pre-Pandemic Population (p=0.74)
- Per-Protocol Population (p=0.98)

ADAS-Cog-Exec

Treatment-related change from baseline (z-scores)



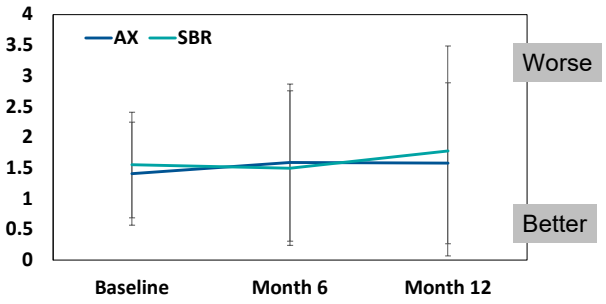
*covariates: site, apoE4, sex

**Scores were lower overall for men and for apoE4 carriers, but no difference by treatment assignment

11

Results: Other Clinical Outcomes

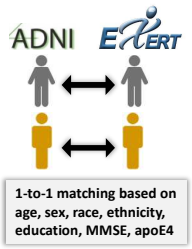
CDR-Sum of Boxes



*** No group differences, and no decline over 12 months**

Same results for Pre-Pandemic Population and for Per-Protocol Population

12

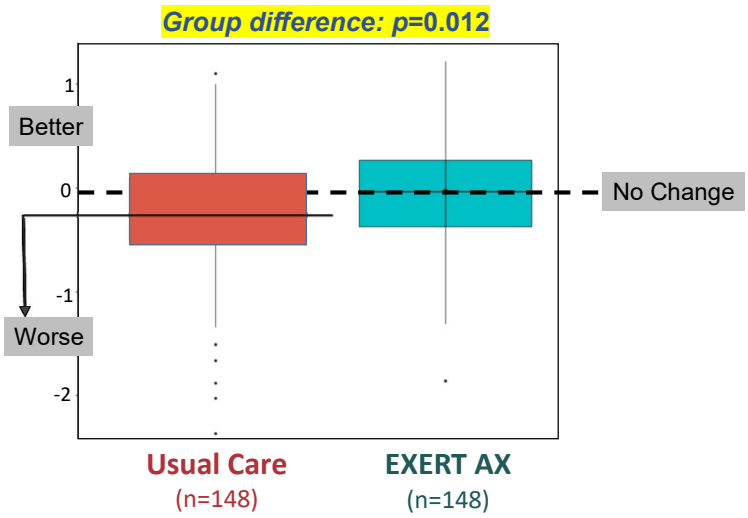


Usual Care Modeling (using ADNI)

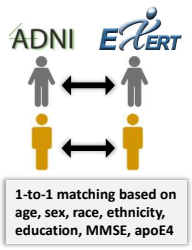
12-Month Change on ADAS-Cog-Exec (z-scores)

ADNI Usual Care group got worse over 12 months …

EXERT Aerobic group did not



13

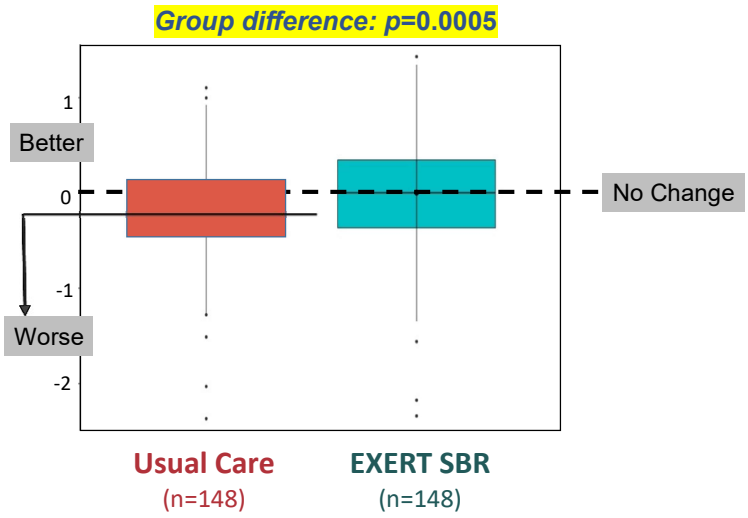


Usual Care Modeling (using ADNI)

12-Month Change on ADAS-Cog-Exec (z-scores)

ADNI Usual Care group got worse over 12 months …

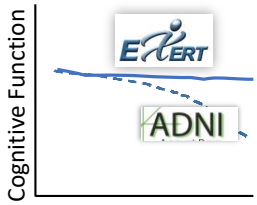
EXERT Stretching, Balance, Range of Motion group did not



14

Summary

- Primary hypothesis was not supported: no group differences in cognitive response to exercise.
- However, cognitive function in adults with aMCI did not decline over 12 months for either exercise group. This differed from the modeled trajectory for matched ADNI 'usual care' cohorts showing 12-month declines on our primary outcome.

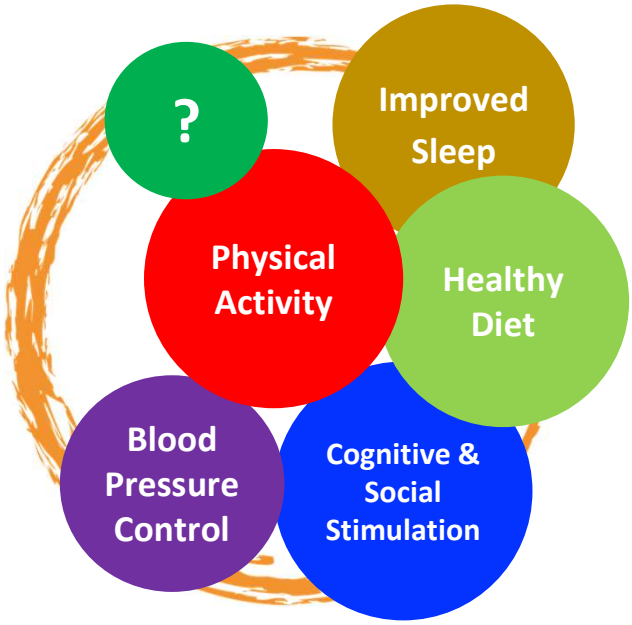


- **Findings suggest that any regular supported exercise of at least 120-150 minutes per week for 12 months may increase resistance or resilience to cognitive decline for MCI.**
- ***Trial was conducted during a pandemic → has implications for durability of intervention with potential resistance to cognitive decline despite other significant life challenges that adults with MCI will face now and in the future.***

15

Combination Therapy ??

- May increase overall 'DOSE' of lifestyle 'medicine'
- Allows for personalized TAILORING of the lifestyle program for cultural practices, physical limitations and logistical challenges



16

Lancet 2015; 385: 2255–63

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto

FINGER

N = 1260
Age: 60-77 years

MULTIDOMAIN INTERVENTION
- Nutrition
- Exercise
- Cognitive training
- Vascular risk monitoring

2 years

REGULAR HEALTH ADVICE

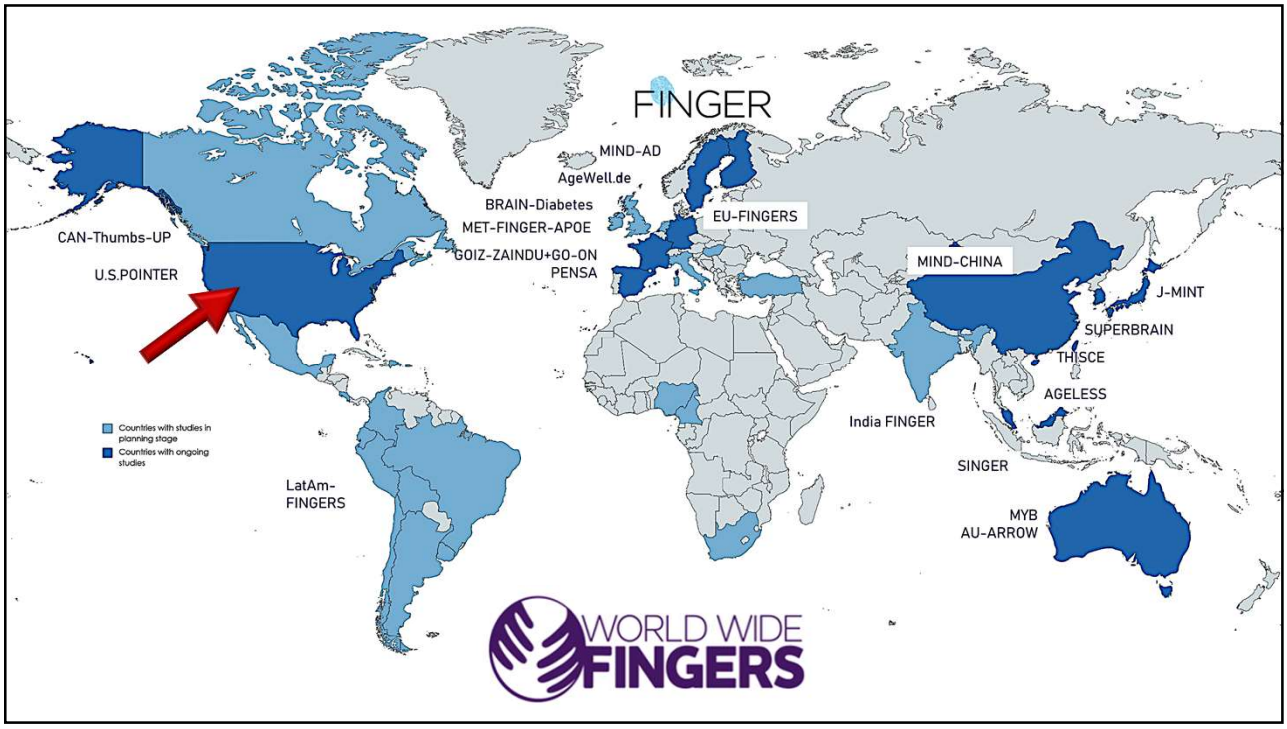
Improved Cognition

Fewer Chronic Illnesses

Less Decline in Function

Extended 10-year follow-up in progress…

17



18

U.S.POINTER ALZHEIMER'S ASSOCIATION

Who?

2000 cognitive normal older adults (60-79 years) at increased risk for cognitive decline due to:

- ✓ Sedentary lifestyle
- ✓ An unhealthy diet (based on a brief diet screener)
- ✓ Suboptimum cardiovascular health
- ✓ Family history of memory problems
- ✓ Race and ethnicity: Black/African American, Native American, Hispanic

What?

Goal: Test the effects of two lifestyle interventions on cognitive function over 2 years.

Intervention Groups

SELF-GUIDED GROUP

- Participants design their own lifestyle intervention program
- Receive education on healthy lifestyles and brain health
- Annual health monitoring

STRUCTURED GROUP

- Participants provided with a structured lifestyle intervention program to follow
- Receive education on healthy lifestyles and brain health
- More frequent health monitoring

19

PARTICIPANT CONTACT SCHEDULES

Self-Guided Group

		Year 1 Months												Year 2 Months										
Timeline		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Intervention	Lifestyle Health Education & Support	X[1]		X			C			X			Y C			X			C			X			Y C

Structured Group

		Adoption				Transition		Maintenance																	
		Year 1 Months (Weeks)												Year 2 Months											
Timeline		1 (1-4)	2 (5-8)	3 (9-12)	4 (13-16)	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Intervention Domain	Physical Exercise[1,2]	XXXX				XX OO	XX OO Y C	X O	X O	X O Y	X O	X O	X O Y C	X O	X O	X O Y	X O	X O	X O Y C	X O	X O	X O Y	X O	X O	X O Y C
	Nutrition[3]		XXXX	OO	OO																				
	Cognitive Exercise[4]			XXXX																					
	Medical Monitoring				XXXX																				

U.S.POINTER alzheimer's association

20

COGNITION

Outcomes	Cognitive Domain	Tests
Primary Composite (PmNTB)	Memory	Free and Cued Selective Reminding Test (FCSRT)
		Immediate and Delayed Story Recall (SR)
		Immediate and Delayed Visual Paired Associates (VPA)
	Executive Function & Processing Speed	Number Span Forward, Backward, Sequencing
		Word Fluency by Letter (F, A, S)
		Word Fluency by Category (Animals, Vegetables, Fruits)
		Digit Symbol Substitution (DSST)
		Trail-Making Test, Condition A (Trails A)
		Trail-Making Test, Condition B (Trails B)
Secondary / Experimental	Global	Mini-Mental Status Exam (MMSE)
	Memory	Cogstate One-Card Learning (OCL)
		Cogstate Face Name Associative Memory Exam (FNAME)
		Cogstate Behavioral Pattern Separation of Objects (BPSO)
	Executive Function & Processing Speed	Cogstate Detection (DET) and Identification (IDN)
		Cogstate One Back (OBK)
		Digital Cognition Technologies Clock Drawing (DCTClock)
		BrainHQ Assessment

21

OUTCOMES

1. POINTER Primary Cognitive Outcome
2. APOE genotype, banked DNA, plasma
3. Adjudicated cognitive status (MCI, AD/ADRD)
4. Extensive health phenotyping (cardiovascular, metabolic)
5. Self-report: subjective concerns, mood, sleep, QOL, health care utilization
6. Data sharing and harmonization with other trials, including WW-FINGERS
7. Ancillary studies (Imaging, Vascular, Microbiome, Sleep)

Allows for head-to-head comparisons

FINGER

large pharma studies (A4, AHEAD)

Other non-pharm studies (EXERT)

U.S.POINTER alzheimer's association

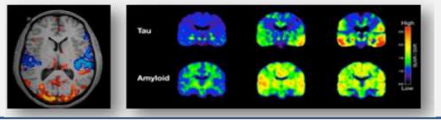
22

NIA-Funded Ancillary Studies

POINTER Brain Imaging Ancillary
(MRI, amyloid/tau PET)

N=1052 (32% URG)

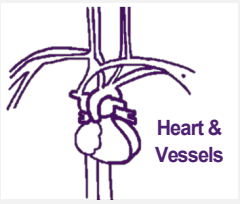
PI: Susan Landau (Berkeley)
NIH/NIA R01AG062689

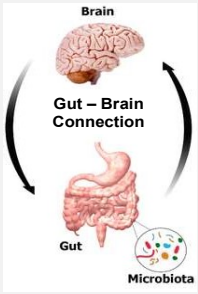


N=480 (32% URG)

POINTER Neurovascular Ancillary
(Ultrasound, Tonometry)

PIs: Tina Brinkley & Hossam Shaltout (Wake Forest)
NIH/NIA R01AG066910





N=807 (34% URG)

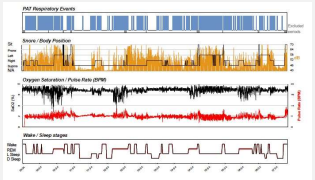
POINTER Gut Microbiome Ancillary
(Metagenomic & Metabolomic Profiling)

PIs: Ali Keshavarzian (Rush), Rima Kaddurah-Daouk (Duke)
NIH/NIA U19AG063744

POINTER Sleep Ancillary (Oximetry, Actigraphy)

PIs: Kate Hayden & Laura Baker (Wake Forest)
NIH/NIA R01AG064440

N=780 (34% URG)



23

Enrollment Closed

Baseline Characteristic At-Risk Cohort	Overall (N=2111)	North Carolina (N=404)	Northern California (N=413)	Chicagoland (N=463)	Houston (N=455)	Rhode Island (N=376)	p-value
Age [in years]	68.2 +/- 5.2	67.8 +/- 5.0	67.5 +/- 5.2	68.5 +/- 5.0	68.5 +/- 5.2	68.4 +/- 5.3	0.41
Age: >= 75 years	274 (13.0%)	47 (11.6%)	46 (11.1%)	59 (12.7%)	67 (14.7%)	55 (14.6%)	<0.001
Age: >= 70 years	903 (42.8%)	159 (39.4%)	151 (36.6%)	220 (47.5%)	201 (44.2%)	172 (45.7%)	0.001
Female %	1453 (68.8%)	308 (76.2%)	277 (67.1%)	315 (68.0%)	299 (65.7%)	254 (67.6%)	0.009
Race/Ethnicity: Participants of Color	647 (30.8%)	117 (29.1%)	124 (30.2%)	145 (31.5%)	206 (45.4%)	55 (14.7%)	<0.001
Education: Not a College Graduate	633 (30.0%)	148 (36.6%)	125 (30.3%)	111 (24.0%)	146 (32.1%)	103 (27.4%)	
Area Deprivation Index - National	36.1 +/- 23.1	56.0 +/- 22.0	20.8 +/- 14.9	33.2 +/- 20.6	39.3 +/- 24.3	31.5 +/- 16.5	<0.001
Systolic Blood Pressure (mmHg)	131.1 +/- 15.9	132.0 +/- 16.5	128.4 +/- 14.0	130.4 +/- 15.7	135.0 +/- 16.0	129.2 +/- 16.6	0.56
Diastolic Blood Pressure (mmHg)	76.7 +/- 9.4	76.0 +/- 9.9	77.5 +/- 9.9	76.2 +/- 9.1	80.1 +/- 7.5	73.1 +/- 9.3	0.11
HBA1C %	5.9 +/- 0.7	5.9 +/- 0.8	5.9 +/- 0.7	5.8 +/- 0.7	6.0 +/- 0.7	5.9 +/- 0.6	0.22
Total Cholesterol mg/dL	193.7 +/- 42.5	200.5 +/- 41.7	201.1 +/- 42.8	189.0 +/- 41.2	189.5 +/- 41.6	189.0 +/- 43.8	<0.001

24

Intervention Adherence: Meeting Goal

SELF-GUIDED GROUP

- Participants design their own lifestyle intervention program
- Receive education on healthy lifestyles and brain health
- Annual health monitoring

- Team Meeting attendance (goal=80%): >90%

STRUCTURED GROUP

- Participants provided with a structured lifestyle intervention program to follow
- Receive education on healthy lifestyles and brain health
- More frequent health monitoring

- Team Meeting attendance (goal=80%): 92%
- Participants logging data (goal=80%): 86%
- Median aerobic exercise min/week (goal=120): 137 min
- Median Fitbit very active min/week (goal=90): 90 min
- Mean MIND diet score (goal=9.5): 10.6

Retention

- Active for assessments: 97%
- Active in intervention 83%

25

U.S. POINTER DATA: Results expected Summer 2025

1. Multiple traditional and experimental cognitive outcomes
2. APOE genotype and blood AD biomarkers (Robert Rissman, ATRI/USC)
3. Stored DNA and plasma for future investigations
4. Adjudicated cognitive status (MCI, AD/ADRD)
5. Extensive health phenotyping (cardiovascular, metabolic)
6. Multiple measures of subjective experience (memory, mood, sleep, QOL)
7. Extensive ancillary study data:
   - Brain amyloid/tau PET, volumetric and ASL MRI
   - Peripheral- and neuro-vascular metrics
   - Gut microbiome, metagenomic, metabolomic data
   - Sleep apnea, sleep fragmentation and other objective measures of sleep quality

26

U.S. POINTER
ALZHEIMER'S ASSOCIATION

Funding

ALZHEIMER'S ASSOCIATION

- U.S. POINTER (parent trial)

NIH National Institute on Aging

- U.S. POINTER – Brain Imaging
- U.S. POINTER – Sleep
- U.S. POINTER – Neurovascular
- U.S. POINTER – Microbiome

Leadership (*plus many others who make this work possible)

Wake Forest School of Medicine
Laura Baker, PhD
Mark Espeland, PhD
Nancy Woolard
Jeff Katula, PhD
Sam Lockhart, PhD
Kate Hayden, PhD
Hossam Shaltout, PhD
Tina Brinkley, PhD
Jo Cleveland, MD
Jeff Williamson, MD

Baylor College of Medicine & Kelsey Research Foundation
Valory Pavlik, PhD
Melissa Yu, MD
Ashley Alexander

Brigham & Women's Hospital
Kate Papp, PhD

UC Berkeley
Susan Landau, PhD

Duke University
Rima Kaddurah-Daouk, PhD

USC / ATRI
Rema Ramen, PhD
Robert Rissman, PhD

Alzheimer's Association
Maria Carrillo, PhD
Heather Snyder, PhD
Katherine Lambert
Claire Day
Terrianne Reynolds, Olivia Montego
Richard Elbein, Ann Marie McDonald
Susan Antkowiak

Karolinska Institutet & National Institute for Health & Welfare
Miia Kivipelto, MD PhD

Rush Medical Center & Advocate Health Care
Martha Clare Morris, ScD
Christy Tangney, PhD
Darren Gitelman, MD
Jennifer Ventrelle, MS
Sarah Graef, MS

U of California – Davis
Rachel Whitmer, PhD
Sarah Farias, PhD

Brown/Butler & Miriam Hospitals
Stephen Salloway, MD
Rena Wing, PhD

27

SUMMARY:

Risk Reduction Through Non-Pharmacological Intervention

- Regular physical exercise may slow cognitive decline in adults at risk for dementia
- U.S. POINTER – a large, diverse, and representative rigorous trial will provide new multi-domain data to inform future implementation of non-pharm strategies to prevent cognitive decline and dementia in at-risk older adults

28