Next Generation of Multidomain Lifestyle Clinical Trials

Design & Implementation for Proof of Concept & Pragmatic Sustainability

Laura Baker, PhD

Wake Forest® School of Medicine

Internal Medicine-Geriatrics, Neurology, & Public Health Sciences
Associate Director, Wake Forest Alzheimer's Disease Center

DISCLOSURES

Funding

- Alzheimer’s Association
- NIA

THE WALL STREET JOURNAL.

What Science Tells Us About Preventing Dementia

There are no instant, miracle cures. But recent studies suggest we have more control over our cognitive health than we might think. It just takes some effort.

Certain factors that could contribute to dementia risk are also things that people can control, like diet and exercise. Credit: Jens Bonnke

By Anne Tergesen

November 17, 2019, 10:30 a.m. EST

1. **Blood Pressure Control**
2. **Exercise**
3. **Cognitive Training**
4. **Diet**
5. **Sleep**
6. **Combination**

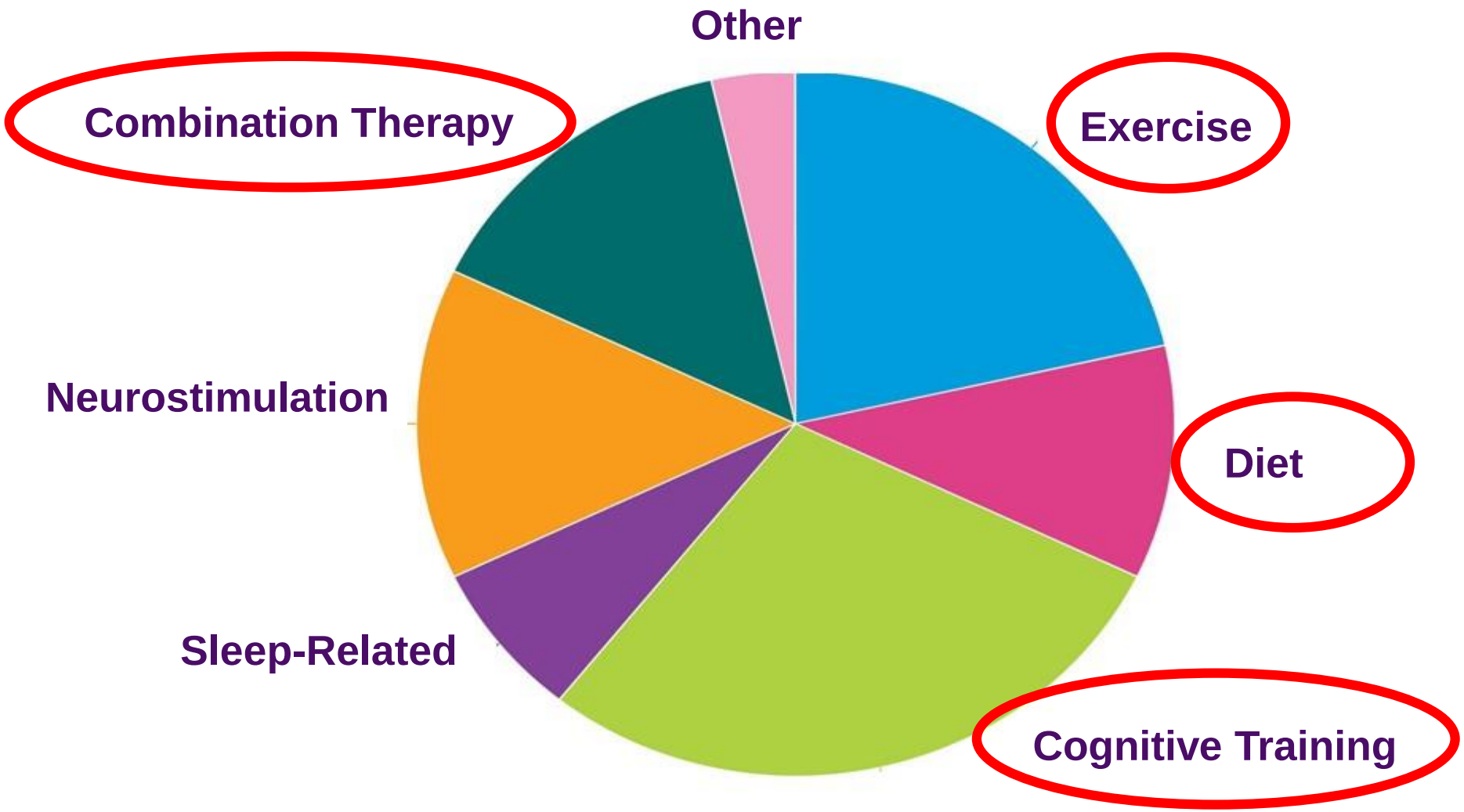
RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO GUIDELINES

World Health Organization

Evidence review	
Physical activity	Overweight
Tobacco	Hypertension
Alcohol	Dyslipidemia
Diet	Diabetes
Cognitive Training	Depression
Social Activity	Hearing loss

2018 & 2019 New NIA AD/ADRD Non-Pharmacological Clinical Trials N = 29



↓ cholesterol

Reduces stress & improves mood

Exercise

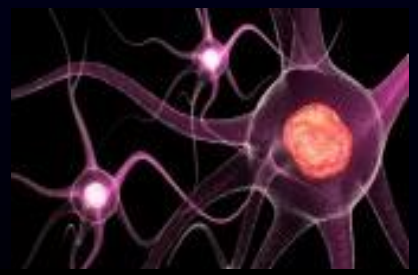
type 2 diabetes

↓

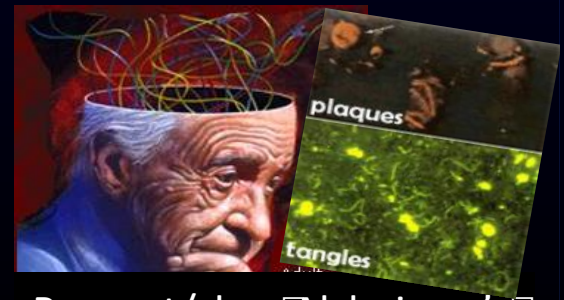
?

In the Brain…

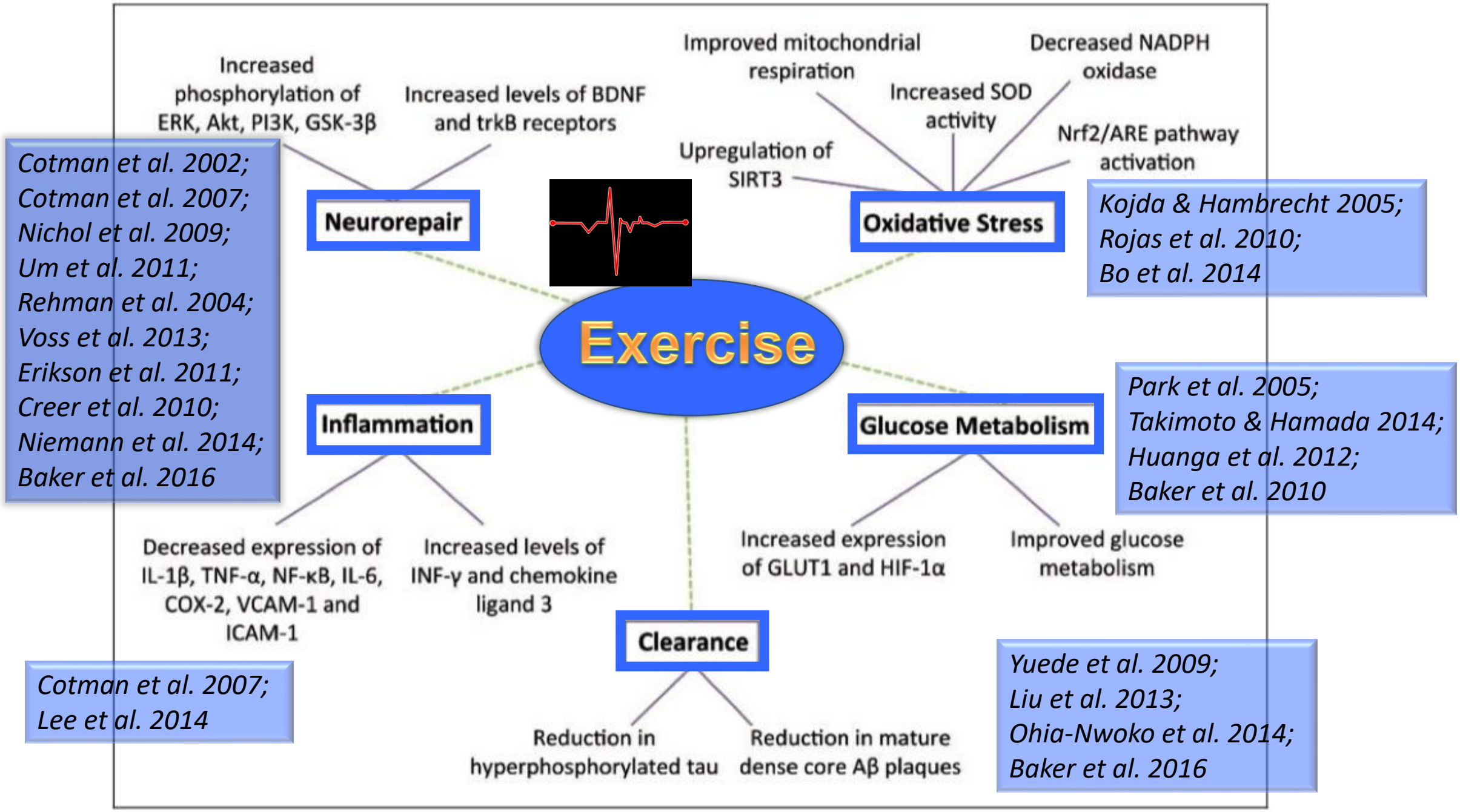
Promote new connections



Resistance to injury & death



Prevent/slow Alzheimer's



Cotman et al. 2002;
Cotman et al. 2007;
Nichol et al. 2009;
Um et al. 2011;
Rehman et al. 2004;
Voss et al. 2013;
Erikson et al. 2011;
Creer et al. 2010;
Niemann et al. 2014;
Baker et al. 2016

Kojda & Hambrecht 2005;
Rojas et al. 2010;
Bo et al. 2014

Park et al. 2005;
Takimoto & Hamada 2014;
Huanga et al. 2012;
Baker et al. 2010

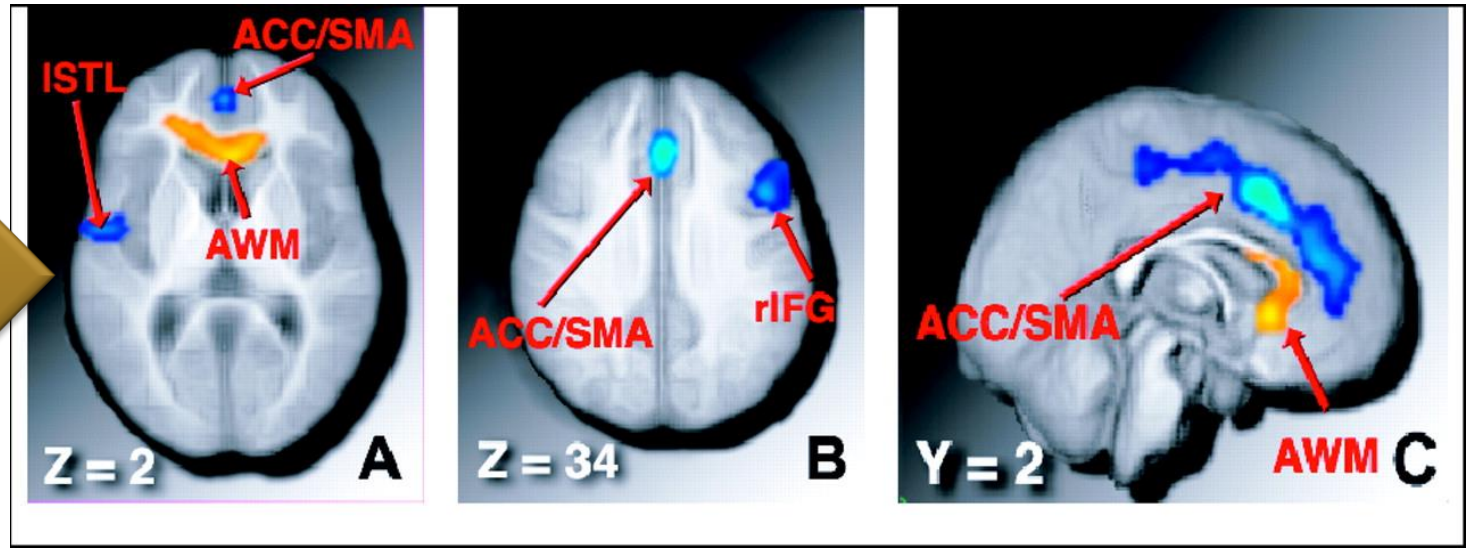
Cotman et al. 2007;
Lee et al. 2014

Yuede et al. 2009;
Liu et al. 2013;
Ohia-Nwoko et al. 2014;
Baker et al. 2016

Trigani & Hamel. J Cerebral Blood Flow & Metab 2017

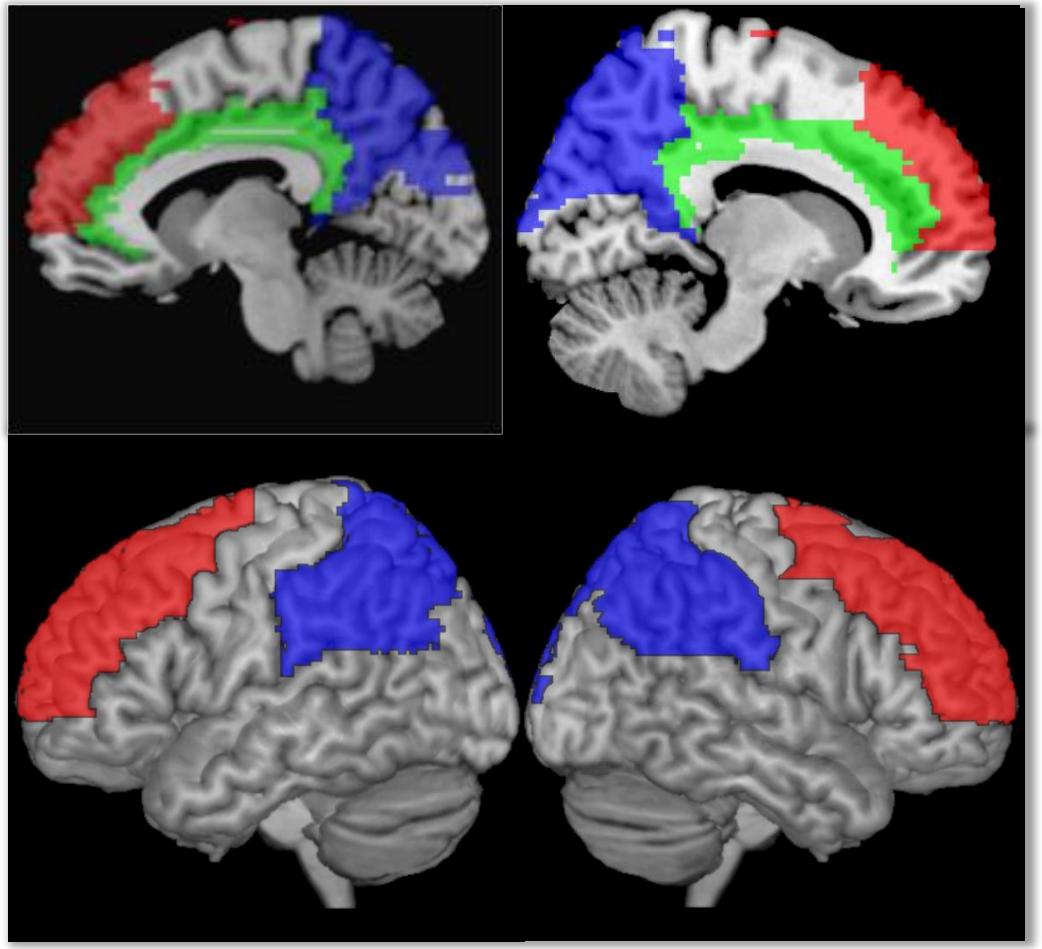
++ Exercise Effects on Brain in Cognitively Normal Older Adults

Brain volume increased with 6 months of aerobic exercise
(Colcombe et al, 2006)

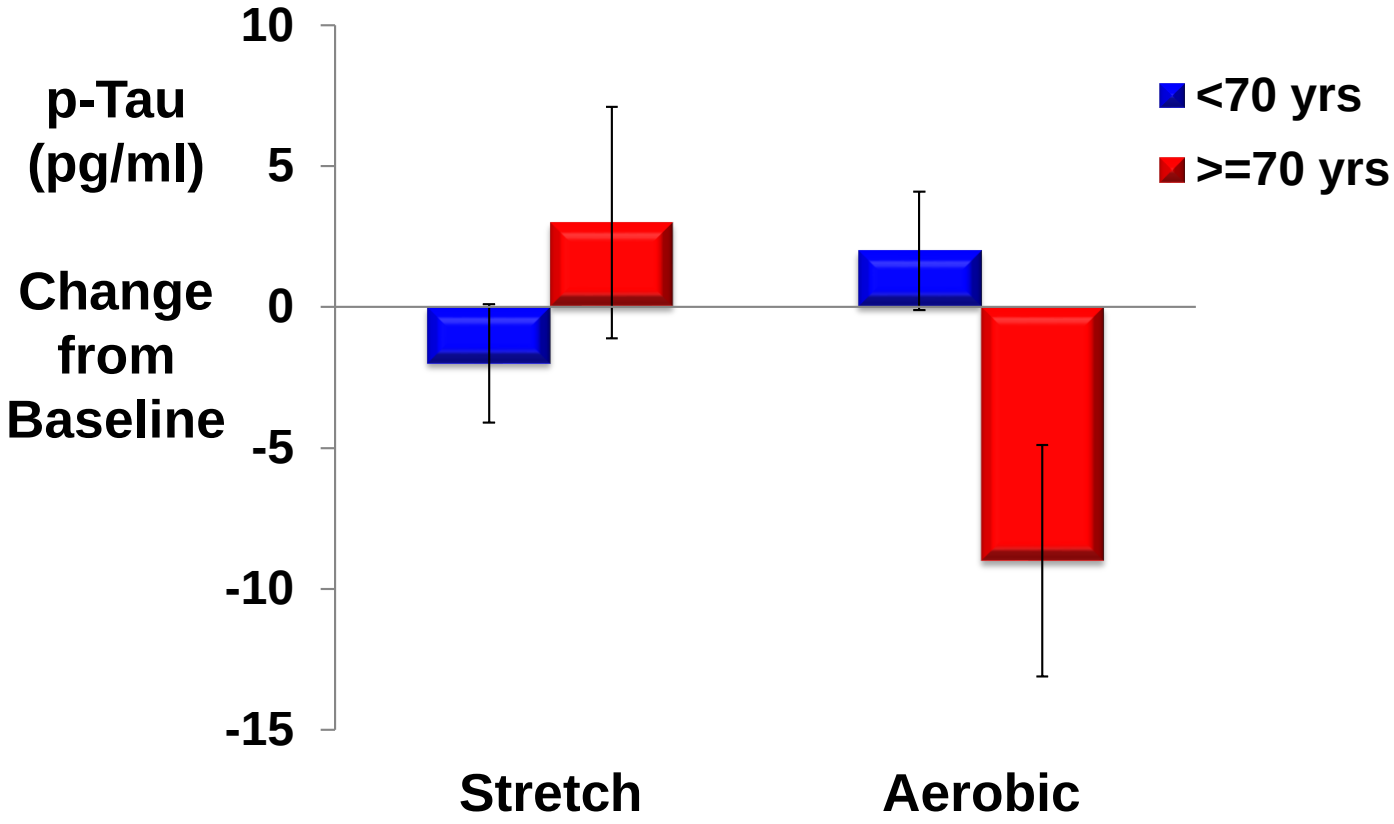


++ cognitive signal to exercise in RCTs also reported for adults with lower cognitive scores & subjective complaints (Lautenschlager 2008) **and in adjudicated MCI** (Baker 2010)

In MCI: 6 mos of aerobic exercise vs. stretching control increased blood flow in brain regions compromised by aging & AD



Aerobic exercise reduced p-Tau levels in CSF in older participants – those with higher levels at baseline

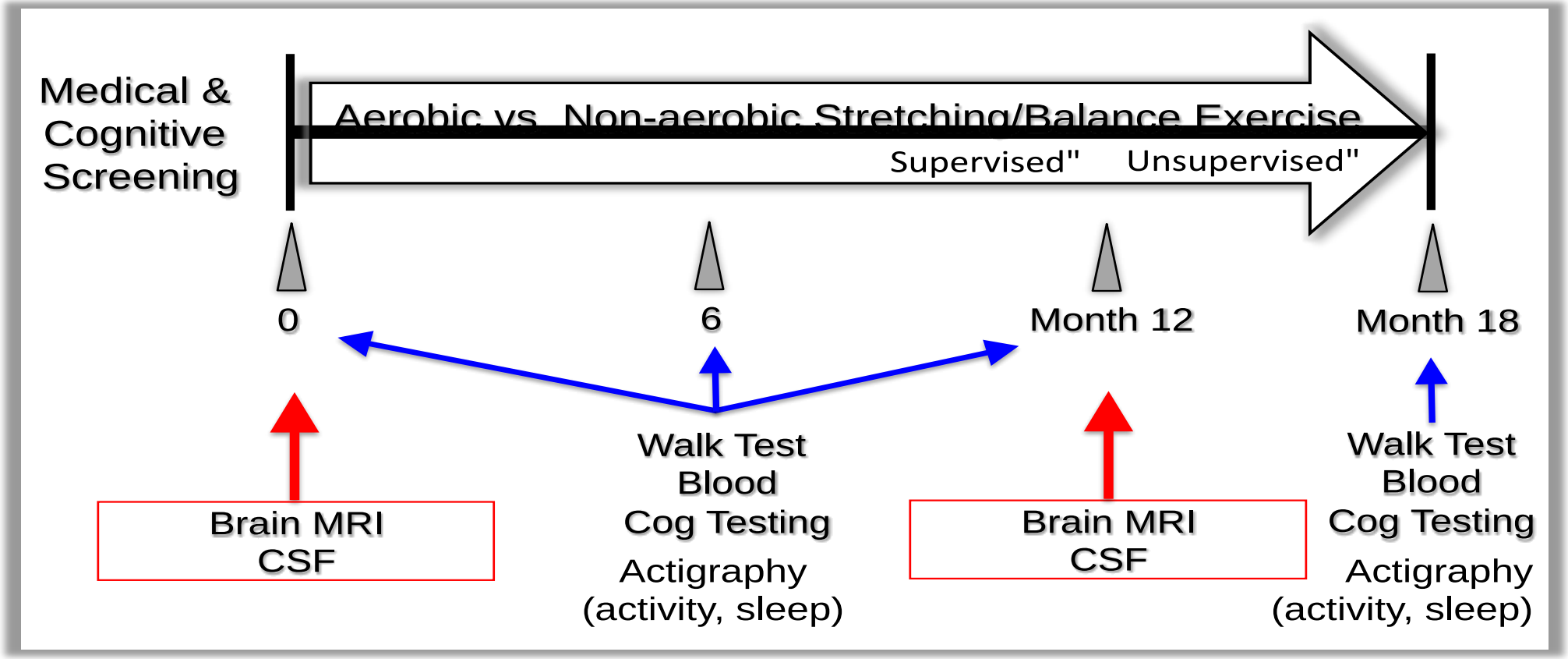


(Baker et al, 2016)

NIA U19 AG010483

STUDY DESIGN

Multi-site RCT; N=300 sedentary adults (65-89 yrs) with MCI



Large scale effort: >170 investigators and staff involved

↓ cholesterol

Reduces stress & improves mood

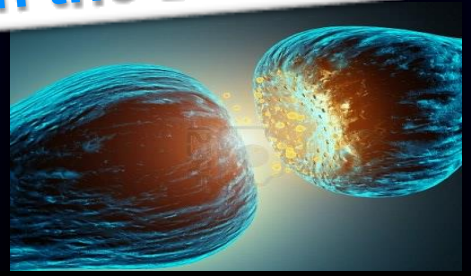
Diet

type 2 diabetes

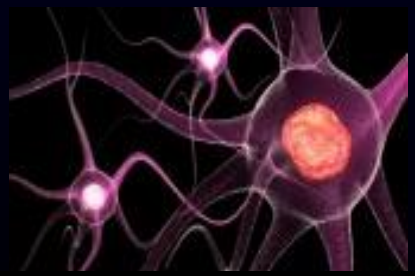
↓

?

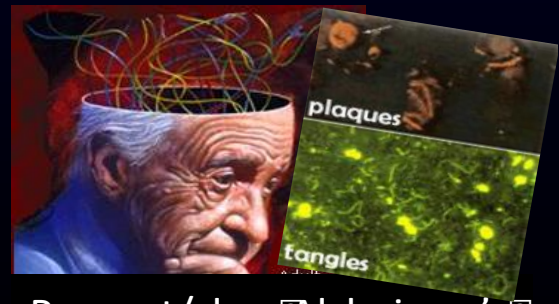
In the Brain…



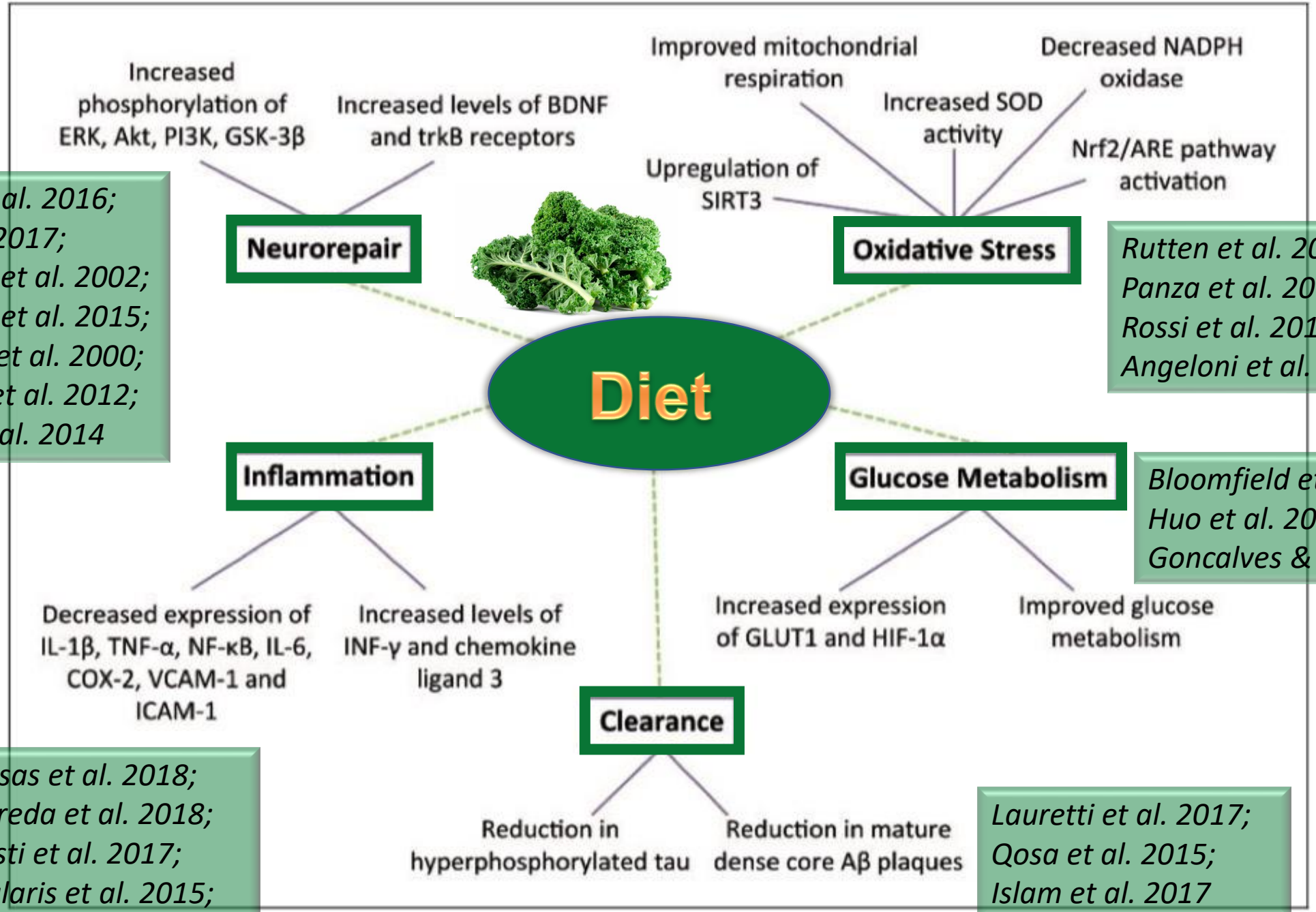
Promote new connections



Resistance to injury & death



Prevent/slow Alzheimer's



Carito et al. 2016;
Qi et al. 2017;
Mattson et al. 2002;
Moosavi et al. 2015;
Tsukada et al. 2000;
Jackson et al. 2012;
Cutuli et al. 2014

Rutten et al. 2002;
Panza et al. 2006;
Rossi et al. 2017
Angeloni et al. 2017

Bloomfield et al. 2016;
Huo et al. 2015;
Goncalves & Amiot 2017

Casas et al. 2018;
Sureda et al. 2018;
Tosti et al. 2017;
Halaris et al. 2015;
Mattson et al. 2008

Lauretti et al. 2017;
Qosa et al. 2015;
Islam et al. 2017

Adapted from Trigani & Hamel. J Cerebral Blood Flow & Metab 2017

Diet May Help Prevent Alzheimer's

March 16, 2015

MIND diet rich in vegetables, berries, whole grains, nuts

Dr. Martha Clare Morris
Rush University

Newly published research suggests that a specific diet called the MIND diet may reduce the incidence of brain disease that increases a person's risk in developing Alzheimer's disease.

The recent study shows that the MIND diet lowered the risk of Alzheimer's by as much as 53 percent in participants who adhered to the diet rigorously, and by about 35 percent in those who followed it moderately well according to a paper published online on March 19 in the journal *Alzheimer's & Dementia: The Journal of the Alzheimer's Association.*

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
Powerful ideas for a healthier world

BRIGHAM AND WOMEN'S HOSPITAL

RUSH

Dr. Martha Clare Morris
Rush University

- Phase III RCT
- 3-year intervention of hybrid Mediterranean and DASH diet
- N=600
- 65+ year old cognitive normal and overweight adults
- Primary outcome: cognitive decline
- At Year 1, retention near 90%

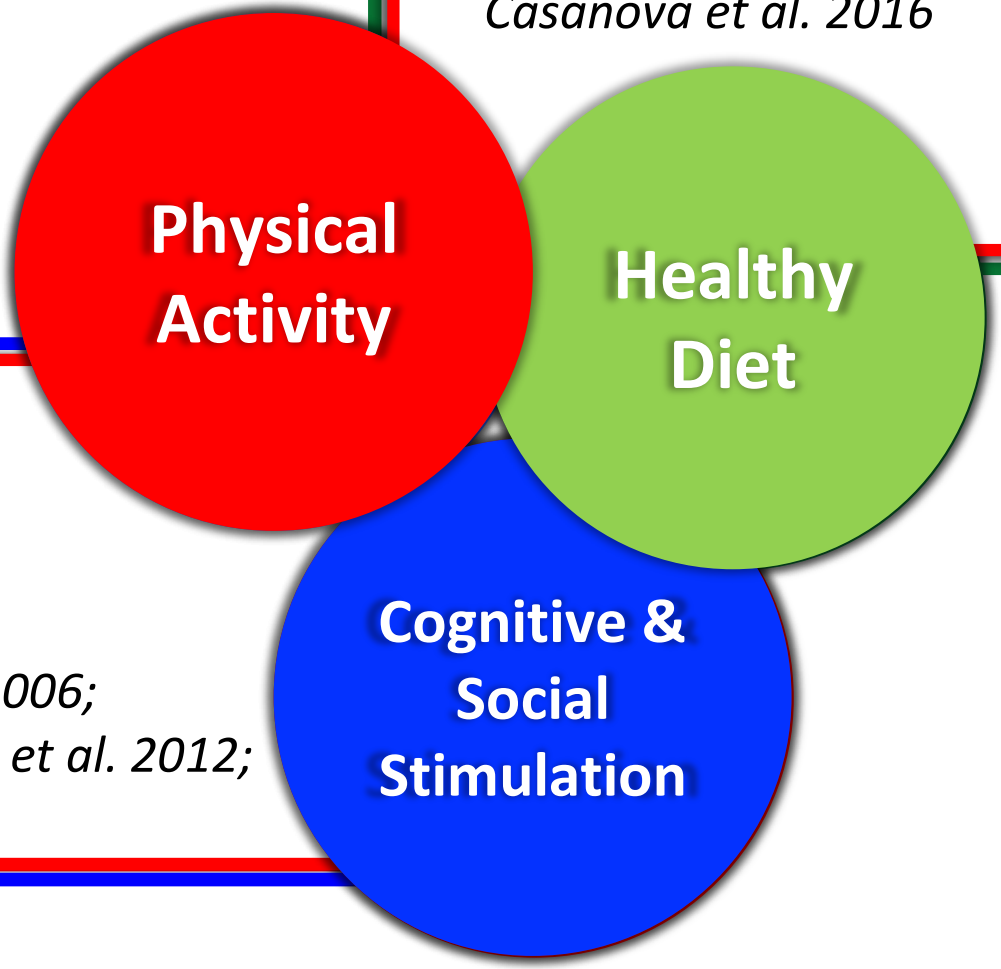
mind

Combination of Lifestyle Interventions …

++Oxidative stress in rodents
Jolitha et al. 2006; Todly et al. 2005

++AD pathology in humans
Baker et al. 2012

++Brain network connectivity in humans
Casanova et al. 2016

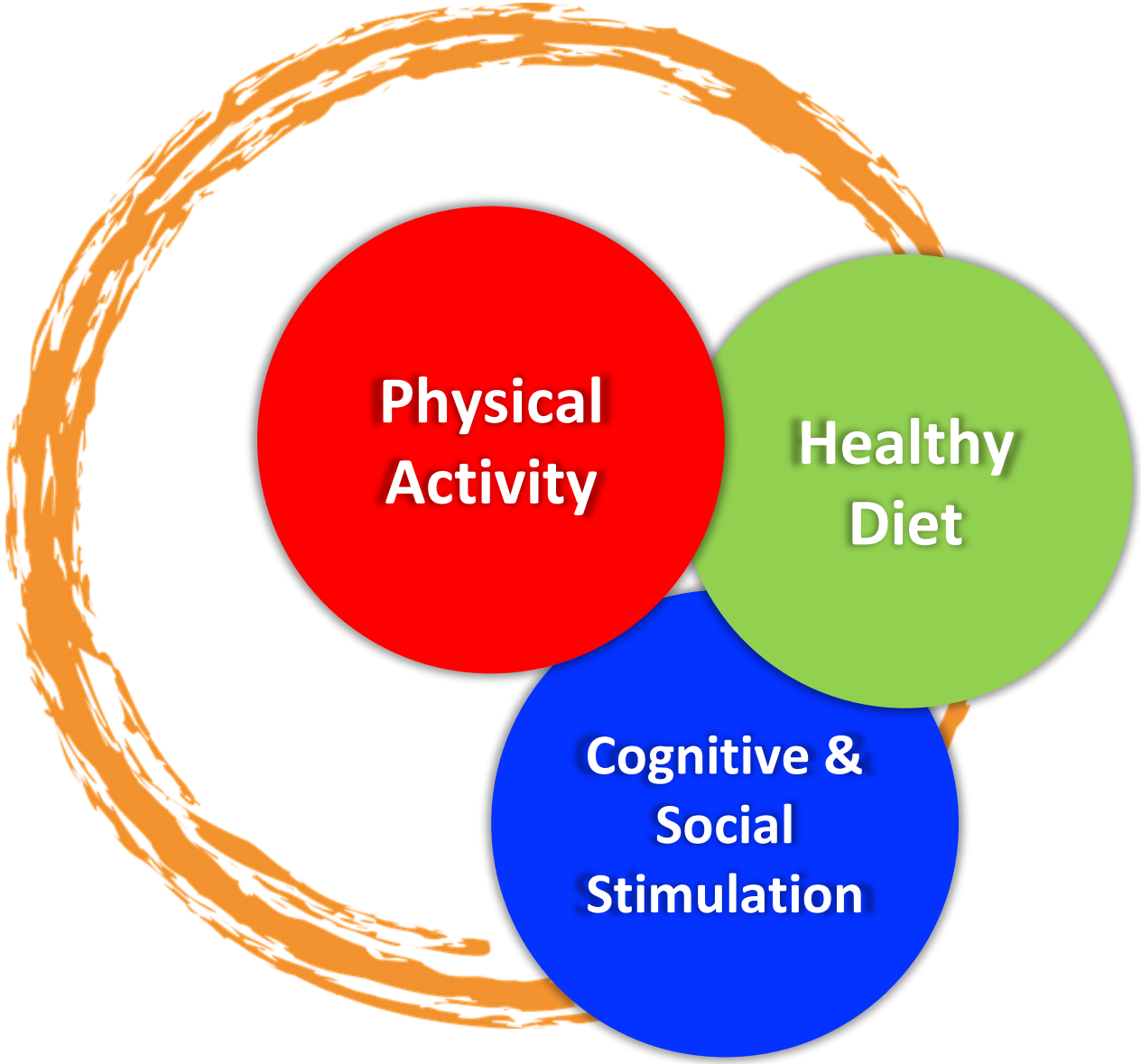


++Cognition in rodents
Langdon & Corbett 2012;
Landon et al. 2013, 2014

++Cognition in humans
Shah et al. 2014; Oswald et al. 2006;
Pieramico et al. 2012; Mortimer et al. 2012;
Karp et al. 2006

Combination Therapy …

- Increases overall lifestyle DOSE?
- Effects more than just additive → SYNERGISTIC?
- Allows for personalized TAILORING of intervention to be sensitive to cultural practices, physical limitations & logistic challenges



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 at risk
Age: 60-77 years

MULTIDOMAIN INTERVENTION

Nutrition

Exercise

Cognitive training

Vascular risk monitoring

2 years

REGULAR HEALTH ADVICE

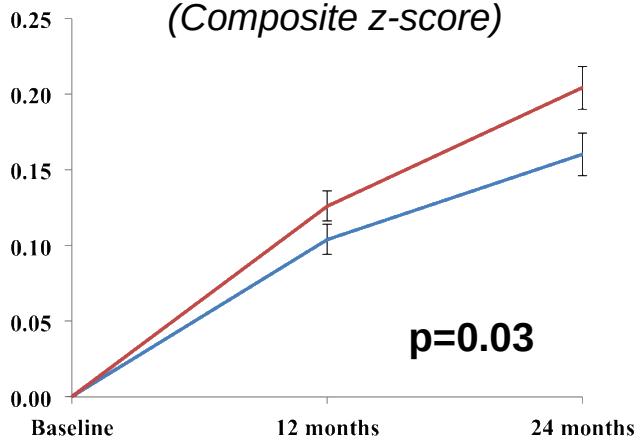
FINGER

Summary of Primary Findings

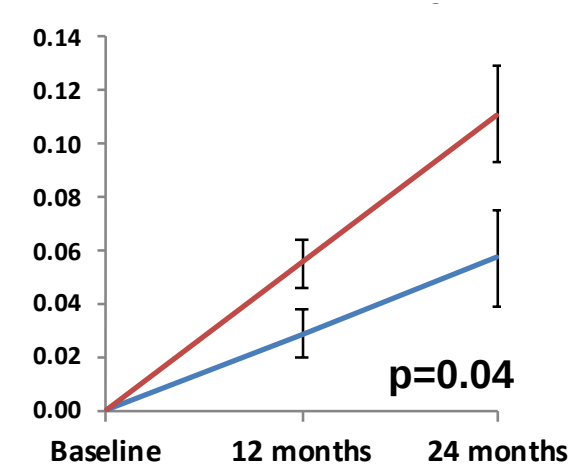
Red - intervention
Blue - control

Primary: NTB Total Score

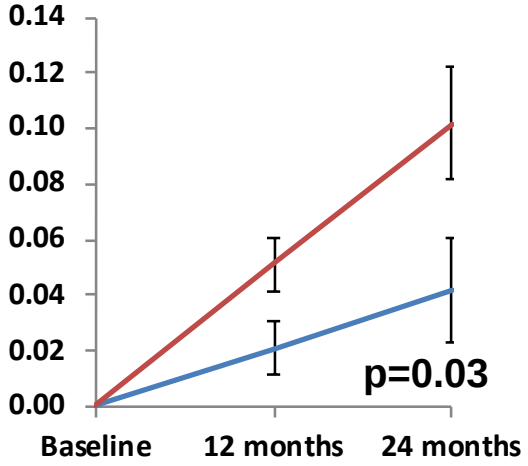
(Composite z-score)



Executive Function

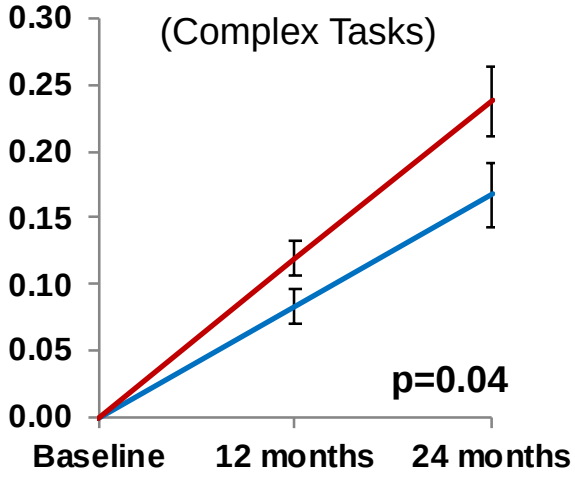


Processing Speed



Memory

(Complex Tasks)



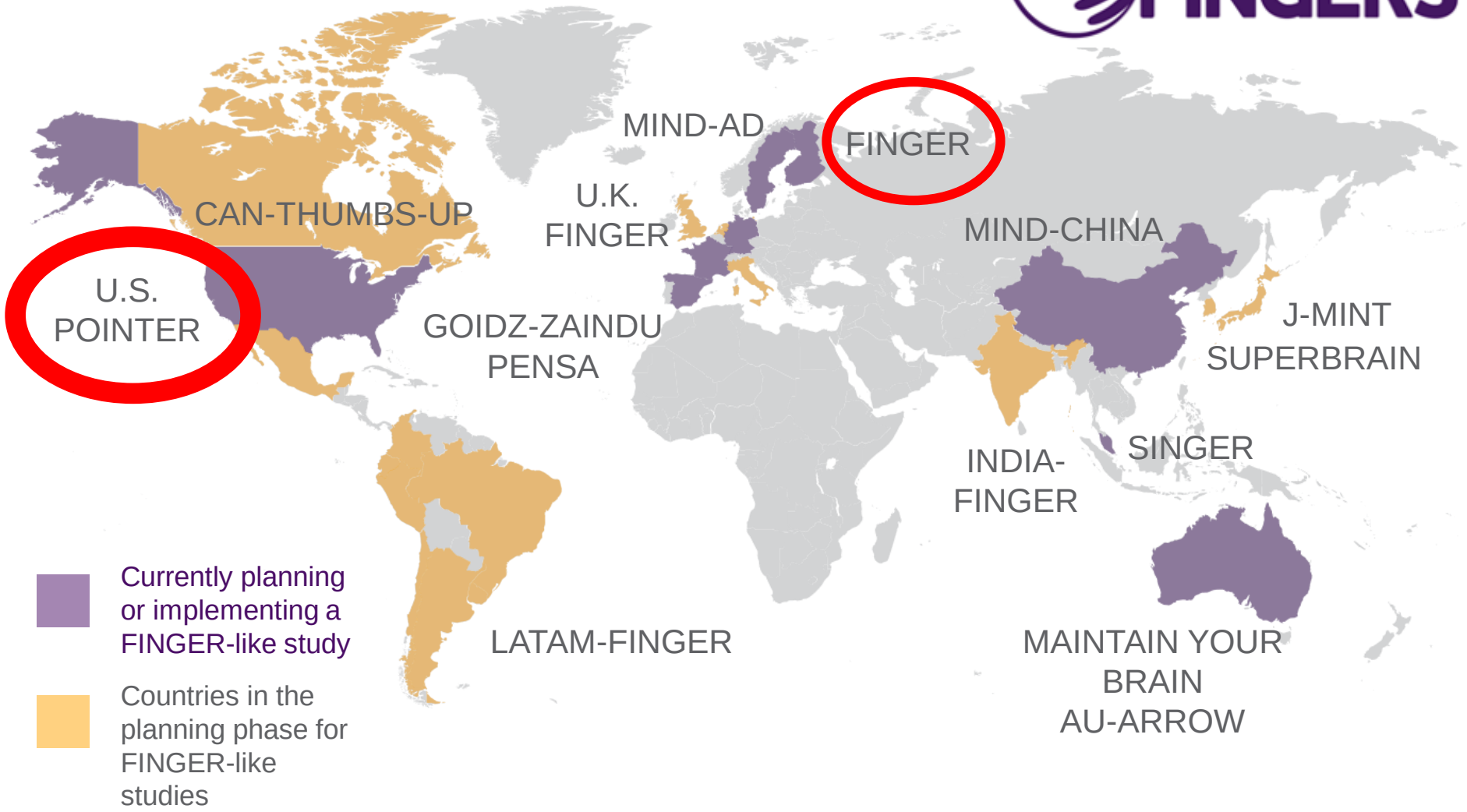
Improvement	**+ 25%**	**+ 83%**	**+ 150%**	**+ 40%**

Ngandu, Kivipelto et al. Lancet 2015

- **Lower risk for cognitive decline**
- **30% lower risk for functional decline (IADL)** (*Kulmala, Kivipelto et al., JAGS 2019*)
- **Better health related quality of life** (*Strandberg, Kivipelto et al, Eur Ger Med 2017*)

GLOBAL EXPANSION

- International network of FINGER-like lifestyle intervention studies
- Allows for harmonization of protocols, outcomes, analyses



U.S.POINTER RESPONSIBILITY TO THE FIELD

- Strengthen potential impact of multi-domain lifestyle intervention using lessons learned from FINGER (Kivipelto is a POINTER investigator)
    - Increase DOSE of intervention through increased ppt accountability & support by trained staff → adherence
- Adapt FINGER lifestyle intervention to American culture to increase likelihood of 'uptake'
- Work with WW-FINGERS and other groups to harmonize intervention delivery and outcomes assessment protocols – with allowances for cultural/country differences → sharing of POINTER resources, help develop "Master" Protocol
- Create an intervention delivery program that could be SUSTAINABLE in the community if the trial results are positive

Participants

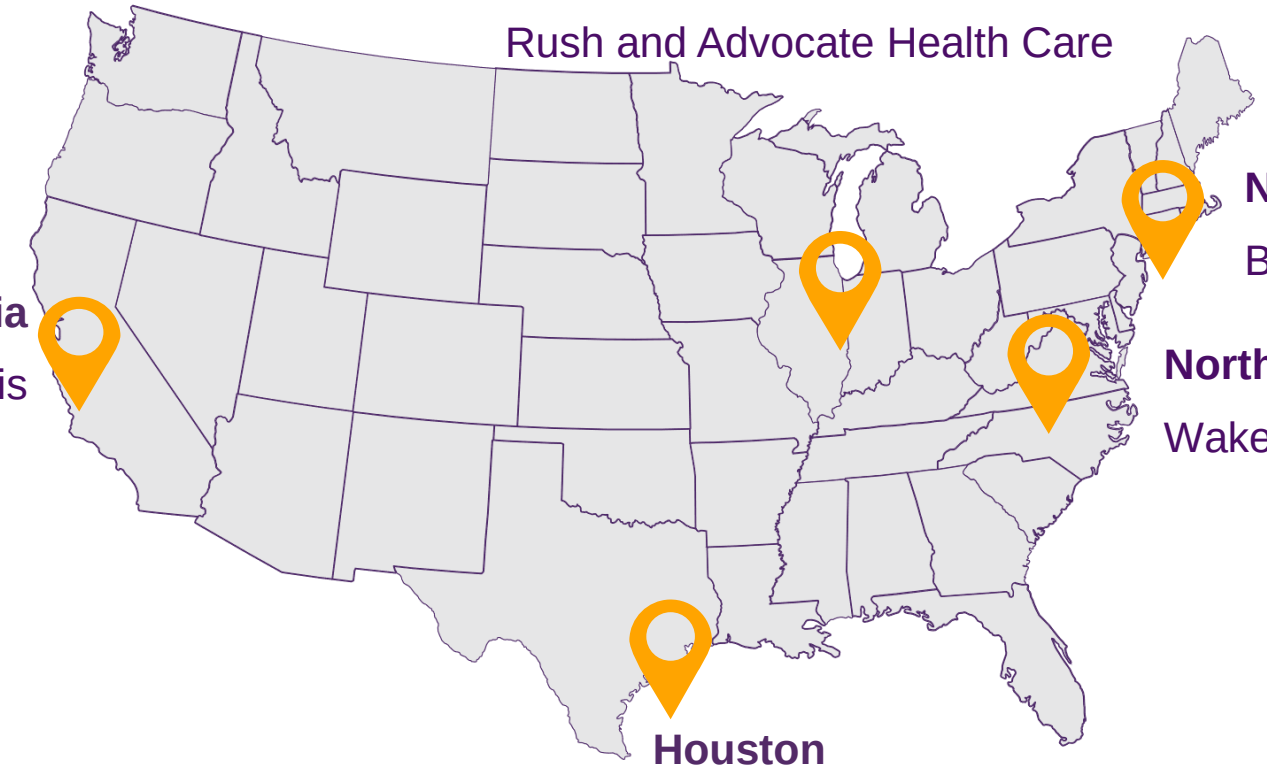
N =2000 cognitively normal older adults (60-79 years) at increased risk for cognitive decline due to:

- ✓ sedentary lifestyle
- ✓ poor diet (high in sat/trans fats, sugar; low in leafy green veggies, berries, fish)
- ✓ suboptimum cardiovascular health status (SBP ≥125, LDL-C ≥115, HbA1c ≥6)
- ✓ 1st degree family history of memory impairment

Primary Aim

Assess effects of random assignment to one of two lifestyle interventions focused on increasing aerobic exercise, adherence to a healthy diet, cognitive and social challenge, and regular health monitoring to manage cardiometabolic risk factors on 2-year cognitive trajectory.

SITES



Chicagoland

Rush and Advocate Health Care

New England - RI

Brown University

Northern California

UC Davis

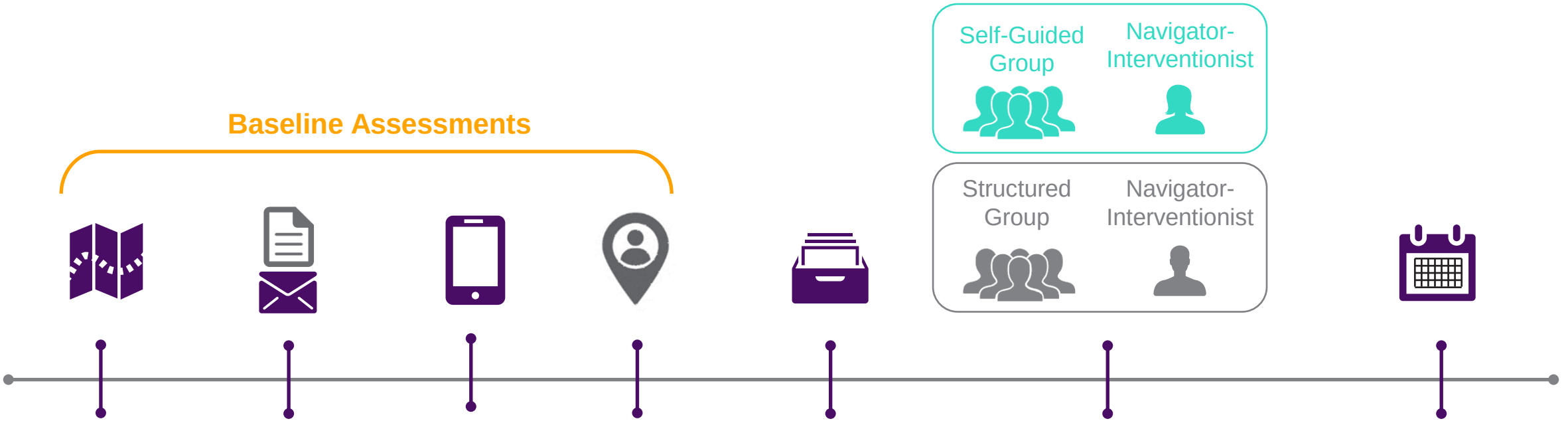
North Carolina

Wake Forest

Houston

Baylor and Kelsey Research

RECRUITMENT → ENROLLMENT



Step 1:
Electronic Medical Record Search and Grassroots Outreach Approach

Step 2:
Mailed Questionnaires

Step 3:
Telephone Interview

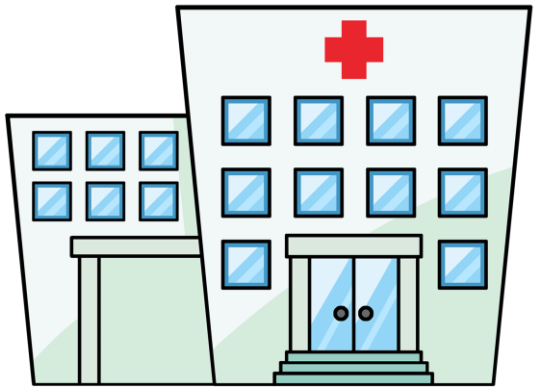
Step 4:
In-person baseline visit

Randomization

Assigned to Teams
of 10-15 ppts

Outcomes Assessments
every 6 months for 2 years

COMMUNITY PARTNERSHIP TO SUPPORT INTERVENTION DELIVERY



Research Clinic

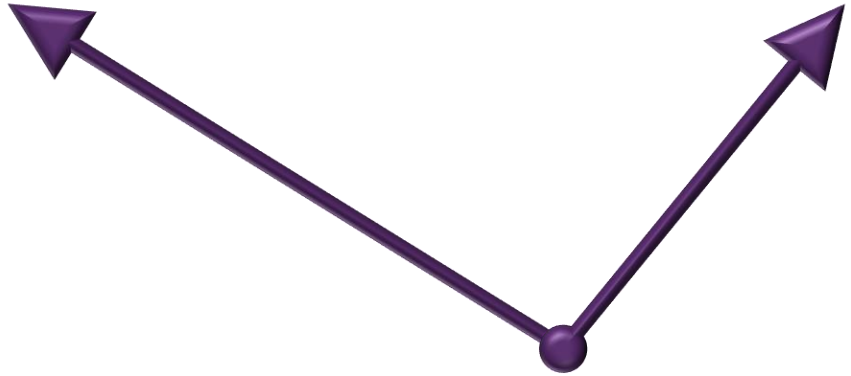
Intervention Oversight

Structured Group	Navigator-Interventionist	Self-Guided Group	Navigator-Interventionist
Structured Group	Navigator-Interventionist	Self-Guided Group	Navigator-Interventionist

Alzheimer's Association Local Chapter

SELF-GUIDED GROUP

STRUCTURED GROUP



Differ in format, expectations, and accountability

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

SELF-GUIDED GROUP

		Year 1 Months												Year 2 Months											
		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											
		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

Cognitive Outcomes

Outcomes	Cognitive Domain	Tests
Primary Composite	**Memory**	Free and Cued Selective Reminding Test
		Story Recall (SR)
		Visual Paired Associates
	Executive Function & Processing Speed	Number Span & Sequencing
		Word Fluency
		Digit Symbol Substitution
		Trails A & B
Secondary / Experimental	**Global**	Mini-Mental Status Exam
	Memory	Cogstate One-Card Learning, Face Name Memory Exam, Behavioral Pattern Separation of Objects
	Executive Function & Processing Speed	Cogstate One Back
		Digital Cognition Technologies Clock Drawing

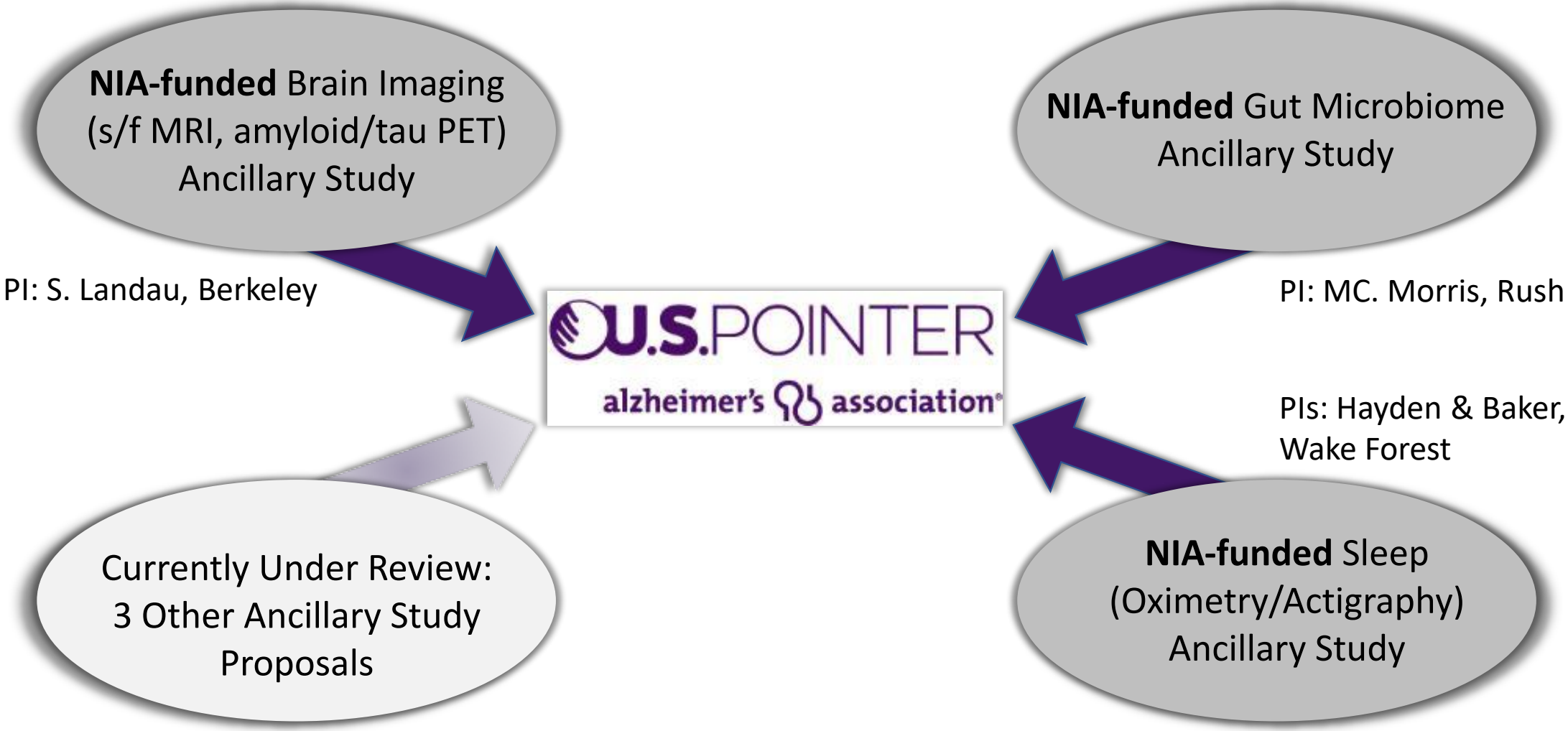
U.S.POINTER alzheimer's association

Outcomes

1. **POINTER Primary Cognitive Outcome**
2. **APOE**
3. **Banked DNA and plasma**
4. **Extensive health phenotyping (cardiovascular, metabolic)**
5. **Self-report: subjective concerns, mood, sleep, QOL, health care utilization**
6. **Ancillary study outcomes**

**** Allows for data sharing and harmonization with other trials, including WW-FINGERS***

Leveraging Parent Trial Resources to Expand Scientific Footprint



U.S.POINTER PROGRESS TO DATE

Sites	IRB & Training	Screening	Baseline	Month 6	Month 12	Month 18	Month 24
N Carolina							
N California							
Chicagoland							
Houston							
New England - RI							

As of Dec 6, 2019 …

Total Screened: **1208**

Total Randomized: **96**

**** Large-scale effort involving more than 150 investigators, staff and community partners***

Future Directions: Moving the Field Forward Using Lifestyle Intervention as Medicine to Protect Brain Health

- For <u>GENERALIZABILITY</u>, need to test whether FINGER findings can be replicated in large heterogeneous populations
- For <u>SUSTAINABILITY</u>, need to adapt lifestyle interventions to fit multiple cultures using a community-based infrastructure for intervention delivery
- For <u>EFFICACY</u>, need large rigorous RCTs using standardized/harmonized methods to test effects of combination lifestyle therapy on brain function – includes testing effects of lifestyle-pharma combination therapies

Study Team

Ancillary Studies

Wake Forest School of Medicine

*Coordinating Center
Laura Baker, PhD
Mark Espeland, PhD
Nancy Woolard
Jing Su, PhD
Scott Rushing
Jeff Katula, PhD
Julia Spell
Iris Leng, PhD
Sam Lockhart, PhD
Ben Williams, MD
Jeff Katula, PhD

*Clinical Site
Jeff Williamson, MD
Jo Cleveland, MD
Bonnie Sachs, PhD

Alzheimer's Association

Maria Carrillo, PhD
Melanie Chavin
Claire Day
Richard Elbein, MA
Katherine Lambert, CFRE
Rey Martinez
Joanne Pike, DrPh
Terrianne Reynolds, MPH, SMP
Heather Snyder, PhD

Baylor College of Medicine / Kelsey Research

*Clinical Site
Valory Pavlik, PhD
Melissa Yu, MD
Michele York, PhD

USC / ATRI

Rema Raman, PhD
Gus Jimenez-Maggiorra
Robert Rissman, PhD

Harvard

Kate Papp, PhD
Dorene Rentz, PhD
Yakeel Quiroz, PhD

Rush Medical Center/Advocate Health Care

*Clinical Site
Martha Clare Morris, ScD
Darren Gitelman, MD
Jennifer Ventrelle, MS
Elizabeth Hartman, PhD
Kristin Krueger, PhD

U of California – Davis

*Clinical Site
Rachel Whitmer, PhD
Sarah Farias, PhD
Michelle Chan, PhD

Brown University

*Clinical Site
Stephen Salloway, MD
Rena Wing, PhD
Stephen Correia, PhD

Karolinska Institute & National Institute for Health & Welfare

Miia Kivipelto, MD PhD
Tiia Ngandu, MD PhD
Alina Solomon, MD PhD