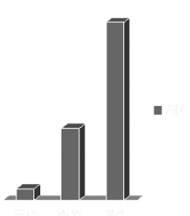
U.S.POINTER
alzheimer's association

# U.S. POINTER: Study Design

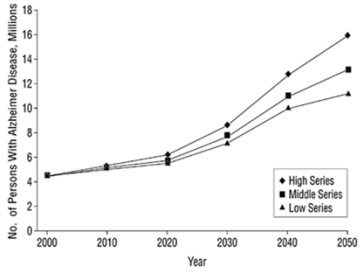
**Martha Clare Morris, Sc.D. for the U.S. POINTER team**
Director, Rush Institute for Healthy Aging and the MIND Center for Brain Health
Rush University, Chicago, IL
Healthy Brain Aging: Risk & Prevention Conference, May 3, 2019
SIU Center for Alzheimer's Disease and Related Disorders, Springfield, IL

## Alzheimer's Disease Prevalence

- Exponential increase with age
- Oldest age categories are fastest growing
- No cure
- Ineffective treatment
- Prevention research critical



## Prevalence of Alzheimer's Disease in U.S.




Hebert LE, et al. *Arch Neurol* 2003;60:1119-1122.

## Alzheimer's Disease Burden

The **BURDEN** is **LARGE**

- **5.5 million with Alzheimer's in the US (projected to be over 14 million by 2030)**
- **$259 billion costs in 2017**
- **Dementia most expensive disease in America**
- **5th leading cause of death among Americans aged 65 and older**

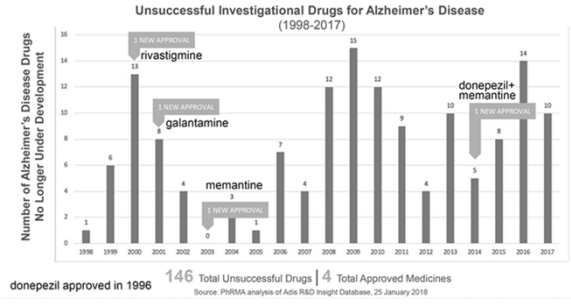
Hurd et al. N Engl J Med. 2013
MMWR Morb Mortal Wkly Rep. 2017
Alz. Dis. Facts and Figures, Alzheimer's & Dementia (2017)

Slide from CDC Grand Rounds: Sarah Lenz Lock, JD

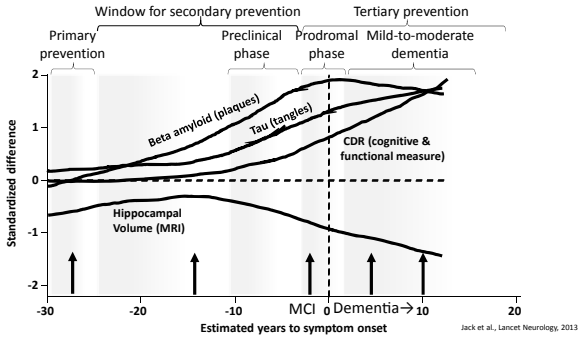
## DRUG TRIALS OF AD

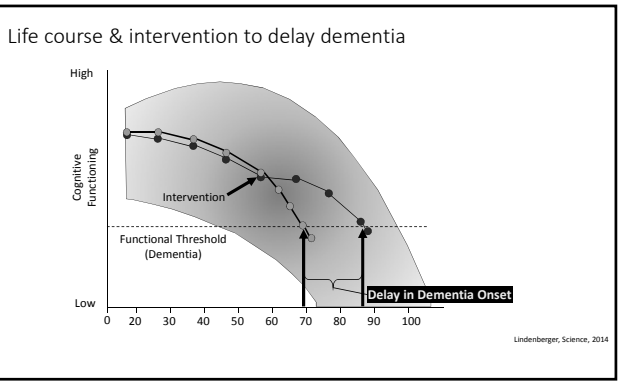
**Drug trials to combat dementia Have Failed**

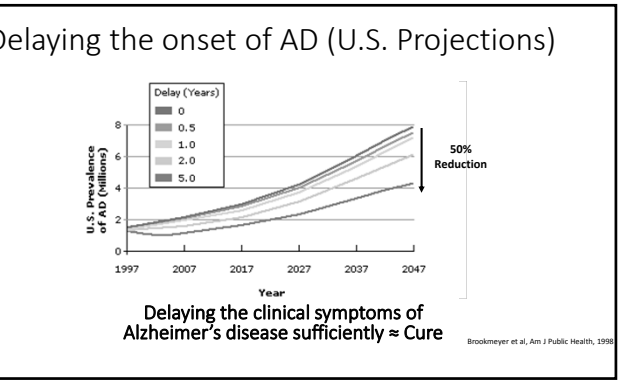
- **Between 2002 and 2012, 413 clinical trials tested 244 compounds.**
- **Only one was approved**
- **Highest failures rates of any disease**
- **99.6%, compared with 81% for cancer.**




Presentation by Greta Stone to PhRMA, 7/27/2018
https://www.alz.co.uk/sites/default/files/conf2018/5_Gretta_Stone_Researching_Alz_disease_medicines.pdf


Window for secondary prevention
Tertiary prevention
Primary prevention
Preclinical phase
Prodromal phase
Mild-to-moderate dementia
Beta amyloid (plaques)
Tau (tangles)
CDR (cognitive & functional measure)
Hippocampal Volume (MRI)
Standardized difference
MCI
Dementia→
Estimated years to symptom onset
Jack et al., Lancet Neurology, 2013


Life course & intervention to delay dementia
High
Low
Cognitive Functioning
Intervention
Functional Threshold (Dementia)
Delay in Dementia Onset
Lindenberger, Science, 2014


Delaying the onset of AD (U.S. Projections)
Delay (Years)
0
0.5
1.0
2.0
5.0
U.S. Prevalence of AD (Millions)
50% Reduction
Year
Delaying the clinical symptoms of Alzheimer's disease sufficiently ≈ Cure
Brookmeyer et al, Am J Public Health, 1998

## Predictors of Late Onset Alzheimer's Disease

| Risk Factors | Protective Factors |
|---|---|
| ❑Age | ❑Exercise |
| ❑Education | ❑Diet |
| ❑APOE-ε4 | ❑Cognitive Activities |
| ❑CVD risk factors | ❑Social participation |
| ❑Obesity | ❑Anti-inflammatory agents |
| ❑Head Injury | ❑Cholesterol/Statins |
| ❑Depression, neuroticism | |

## Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease

Suvi Rovio, Ingemar Kåreholt, Eeva-Liisa Helkala, Matti Viitanen, Bengt Winblad, Jaakko Tuomilehto, Hilkka Soininen, Aulikki Nissinen, Miia Kivipelto

Lancet Neurology, 2005

- 1449 / 2000 participants from previous cardiovascular risk studies.
- Average age 50.1 initially and 71.6 when re-examined
- Asked about activity lasting at least 20-30 min and causing breathlessness and sweating

Odds ratio (or risk) for dementia in active vs. sedentary

| Dementia | Alzheimer's disease |
|---|---|
| 0.48 | 0.38 |

Rovio et al., Lancet Neurol, 2005

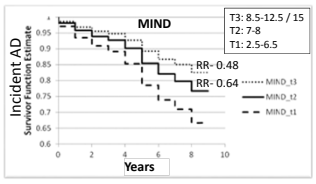
ELSEVIER
Alzheimer's & Dementia

Featured Articles

## MIND diet associated with reduced incidence of Alzheimer's disease

Martha Clare Morris, Christy C. Tangney, Yamin Wang, Frank M. Sacks, David A. Bennett, Neelum T. Aggarwal

- MIND: (Mediterranean-DASH Intervention for Neurodegenerative Delay)
- N=923, given a semi-quantitative food frequency questionnaire




Morris et al., Alz & Dement, 2015

## Social & Leisure activity effects

**Asked about activities and frequency**

- Mental activity: reading, writing, studying, crossword puzzles, painting or drawing
- Physical activity: swimming, walking, or gymnastics
- Social activity: theater, concerts, art exhibitions, traveling, cards/games, or social groups
- Productive activity: gardening, housekeeping, cooking, working for pay after retirement, volunteer work, sewing, knitting, crocheting, or weaving.
- Recreational activity: watching TV or listening to the radio

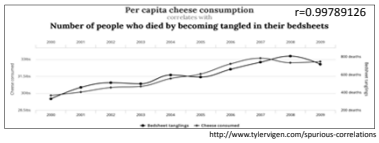
| | No. of dementia cases | RR† | 95% CI† |
|---|---|---|---|
| Mental activity | | | |
| No | 34 | 1 | |
| Less than daily | 40 | 0.81 | 0.52, 1.26 |
| Daily | 49 | 0.54 | 0.34, 0.87 |
| Physical activity | | | |
| No | 114 | 1 | |
| Less than daily | 6 | 0.97 | 0.42, 2.22 |
| Daily | 3 | 0.41 | 0.13, 1.31 |
| Social activity | | | |
| No | 72 | 1 | |
| Less than weekly | 27 | 0.92 | 0.57, 1.47 |
| Daily-weekly | 24 | 0.58 | 0.37, 0.91 |
| Productive activity | | | |
| No | 94 | 1 | |
| Less than weekly | 3 | 0.95 | 0.30, 3.00 |
| Daily-weekly | 26 | 0.58 | 0.38, 0.91 |
| Recreational activity | | | |
| No | 102 | 1 | |
| Less than daily | 6 | 1.06 | 0.46, 2.45 |
| Daily | 15 | 0.95 | 0.55, 1.63 |

- 1,375 subjects in Sweden (mean age: 81.1)
- Follow-up after approx. 7 years.
- Activities assessed by personal interview at recruitment

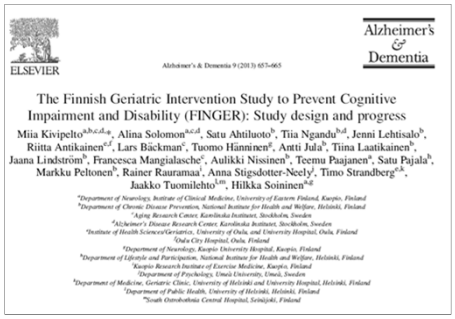
Wang et al., Am J Epidemiology, 2002

## Limitations in past dementia prevention studies

- Lack of Randomized Control Trials
- Single interventions
- Reverse causality – Does the factor cause/cure the disease or vice versa
  - Does exercise prevent dementia or do non-demented people exercise more?
- Communality – common underlying factors
  - Perhaps people who exercise more also have a better diet or are more active
- Correlation vs. causation




http://www.tylervigen.com/spurious-correlations



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Alzheimer's & Dementia

Alzheimer's & Dementia 9 (2013) 657–665

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): Study design and progress

Miia Kivipelto[a,b,c,d,*], Alina Solomon[a,c,d], Satu Ahtiluoto[b], Tiia Ngandu[b,d], Jenni Lehtisalo[b], Riitta Antikainen[e,f], Lars Bäckman[c], Tuomo Hänninen[g], Antti Jula[h], Tiina Laatikainen[h], Jaana Lindström[h], Francesca Mangialasche[c], Aulikki Nissinen[h], Teemu Paajanen[a], Satu Pajala[b], Markku Peltonen[h], Rainer Rauramaa[i], Anna Stigsdotter-Neely[j], Timo Strandberg[e,k], Jaakko Tuomilehto[l,m], Hilkka Soininen[n,g]

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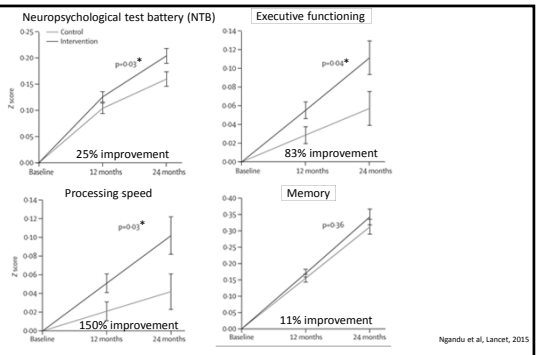
[k]Department of Medicine, Geriatric Clinic, University of Helsinki and University Hospital, Helsinki, Finland
[l]Department of Public Health, University of Helsinki, Helsinki, Finland
[m]South Ostrobothnia Central Hospital, Seinäjoki, Finland

## FINGER study

(Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability)

- Randomized control trial of 1260 adults aged 60-77.
- Cognition at or slightly below expected mean for age (but no dementia)
- Multidimensional intervention vs. general health advice x 2 years.
  - Diet high in fruits, vegetables, whole grains, low-fat mild and meat, fish 2x/week, sucrose < 50g/day
  - Exercise (aerobic, strength, balance) 5x / week
  - Cognitive training: web based 3x / week for 10-15 min and 10 sessions led by a facilitator (educational+status)
  - Social: numerous group meetings
  - Management of metabolic and vascular risk factors.

Ngandu et al, Lancet, 2015

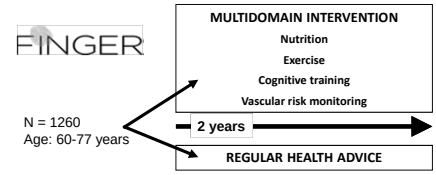


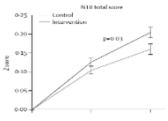

Ngandu et al, Lancet, 2015

*Lancet* 2015; 385: 2255–63

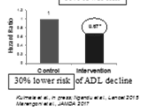
**A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial**

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



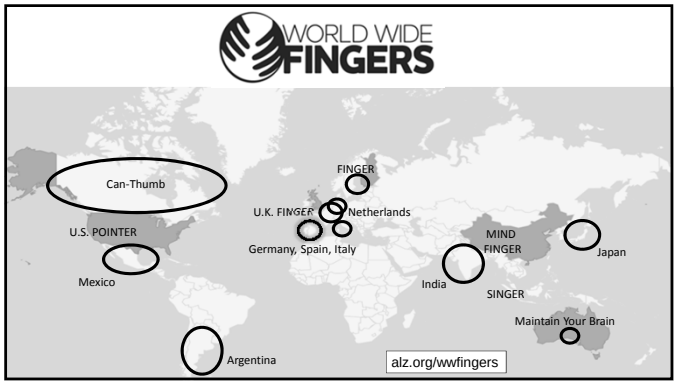




Subsequent Findings




**Interpretation** Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

*Extended 5- & 7-year follow-up ongoing…*



U.S. Study to PrOtect brain health through lifestyle INTErvention to Reduce risk (U.S. POINTER)

– sponsored by the Alzheimer Association

- Two-year clinical trial of 2,000 healthy older adults at risk for cognitive decline
- Tests whether lifestyle intervention can protect cognitive function
- Modeled after the FINGER study
- First study to examine this combined intervention in a large-scale U.S.-based population.

**Intervention Methods will include:**

Physical Exercise

Nutritional Counseling & Modification (MIND)

Cognitive & Social Stimulation

Improved Self-Management of Health Status

## U.S. POINTER Executive Team

**Wake Forest School of Medicine**
***Coordinating Center**
Laura Baker, PhD
Mark Espeland, PhD
Nancy Woolard
Jing Su, PhD
Scott Rushing
Jeff Katula, PhD
Julia Robertson
Iris Leng, PhD
Dan Beavers, PhD
Sam Lockhart, PhD
***Clinical Site**
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Jo Cleveland, MD
Ben Williams, MD
Bonnie Sachs, PhD

**USC / ATRI**
Rema Raman, PhD
Gus Jimenez-Maggiorra
Robert Rissman, PhD

**YMCA**
Valerie Lawson, MS RD

**Karolinska Institutet & National Institute for Health & Welfare**
Miia Kivipelto, MD PhD
Tiia Ngandu, MD PhD
Alina Solomon, MD PhD

**Rush U Medical Center**
Martha Clare Morris, ScD
Jennifer Ventrelle, MS

**U of California – Davis** ***Clinical Site**
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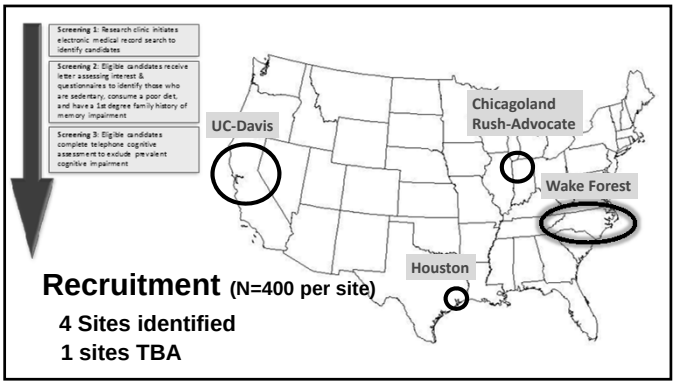
Sarah Farias, PhD,
Charlie DeCarli, MD

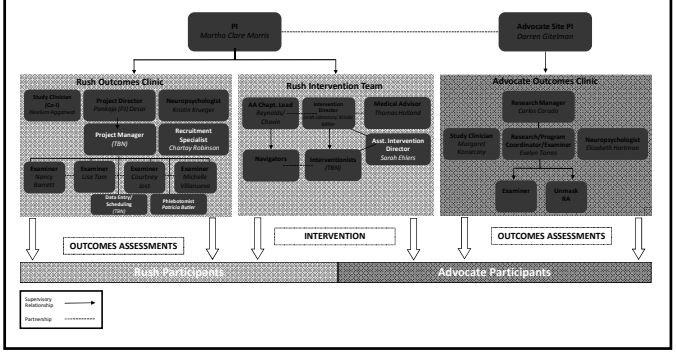
**Brigham & Women's Hospital**
Kate Papp, PhD
Dorene Rentz, PhD
Yakeel Quiroz, PhD

**Alzheimer's Association**
Maria Carrillo, PhD
Heather Snyder, PhD

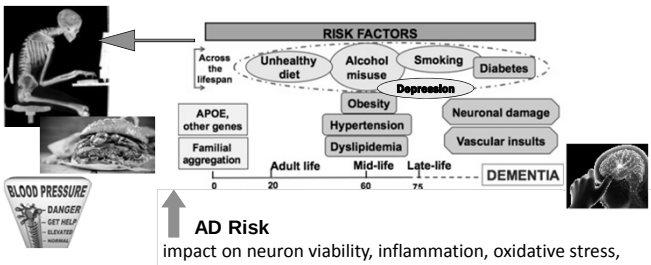



**Recruitment** (N=400 per site)

**4 Sites identified**
**1 sites TBA**



## Healthy and Pathological Aging: Importance of Chronic Exposure to Multiple Factors

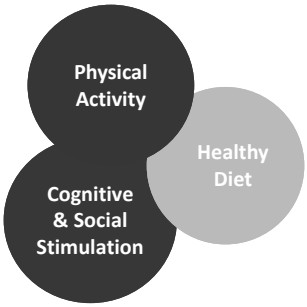



**AD Risk**

impact on neuron viability, inflammation, oxidative stress, glucose metabolism, endothelial cell damage, clearance of tau and β-amyloid from brain

## Interventions to Possibly Reduce Risk…

**Lifestyle Modification & Potential SYNERGISTIC Effects on Brain Health**




## NIA-Commissioned Report by Agency for Healthcare Research & Quality (AHRQ):

**Prevention Recommendations**

**Evidence insufficient – largely because only a few studies have examined interventions with multimodal lifestyle components**

| Intervention | Key Message |
|---|---|
| Multimodal Lifestyle Interventions | • Evidence is insufficient to conclude whether or not multimodal interventions offer benefits for cognitive performance or incidence of MCI or CATD, largely because few studies have examined interventions with similar components.<br>• Low-strength evidence shows that a multimodal intervention composed of diet, physical activity, and cognitive training provides benefits in executive function/attention/processing speed.<br>• Low-strength evidence shows that a multimodal intervention composed of lifestyle advice and drug treatment is not effective in reducing incidence of CATD or benefiting brief cognitive test performance or memory. |

**Low-strength evidence that multimodal intervention provides benefits in executive function, attention, and processing speed**

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**Cohort:**

2000 cognitively normal older adults (60-79 years) at increased risk for cognitive decline due to sedentary lifestyle, poor diet, suboptimum cardiovascular health status, and 1st degree family history of significant memory impairment.

**Primary Aim:**

Assess effects of random assignment to a Self-Guided vs. Structured Lifestyle Intervention focused on increasing aerobic exercise, adherence to the MIND diet, cognitive and social stimulation, and guideline-based health coaching to manage cardiometabolic risk factors on 2-year cognitive trajectory (based on a global cognitive composite outcome).

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## What is the Point of POINTER ?

- To test whether FINGER findings can be replicated in a heterogeneous cohort of older Americans who are at risk for cognitive decline and AD, using a more pragmatic trial approach
- To adapt FINGER lifestyle interventions to fit into American culture
- To identify and develop a community-based infrastructure that could support a sustainable brain health lifestyle program if the trial results are positive

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## Interventions

**Self-Guided Lifestyle Intervention** **Structured Lifestyle Intervention**

Differ in format, expectations, and accountability

## Interventions

**Self-Guided Lifestyle Intervention**

- **Education & Support:** Group meetings 2-3 times per year to provide tangible resources & encouragement to support self-selected plans
- **Guideline-Based Health Monitoring**: Annual physical exam & blood tests

**Structured Lifestyle Intervention**

- **Exercise** (mostly aerobic): 4x per week primarily at a YMCA
- **Nutrition**: MIND diet (modified Mediterranean)
- **Cognitive Stimulation**: Computer cognitive training (BrainHQ), regular group meetings to encourage social/intellectual challenge
- **Guideline-Based Health Coaching**: Frequent exams, blood tests & goal-setting

## Outcomes

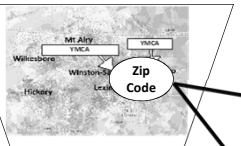
1. **POINTER Primary Cognitive Outcome**
2. **APOE**
3. **Banked DNA and plasma**
4. **Extensive health phenotyping (cardiovascular, metabolic)**
5. **Self-report: subjective concerns, mood, sleep, QOL, health care utilization**
6. **Ancillary studies** (contact Rema Raman: remar@usc.edu)

   Imaging (PET/MRI/fMRI) NIA funded; U19 microbiota NIA pending; actigraphy study (sleep, total activity)
7. **Data sharing and harmonization with other trials, including WW-FINGERS**

## 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 |

1. Electronic Medical Record Search
2. Mailed Questionnaires
3. Telephone Interview




Once Randomized…
Assigned to Teams of 10-15 ppts

SG SG SG

Navigator-Interventionist

STR STR STR

Navigator-Interventionists

**Recruitment** **Baseline Assessments & Randomization**
→ outcomes assessments every 6 months for 2 years

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Heat map of eligible Advocate patients and YMCAs

YMCAs

LGH – Advocate Memory center

35

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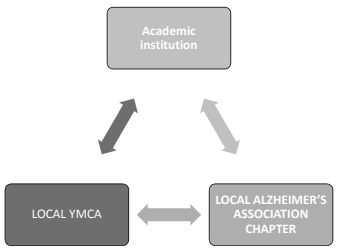
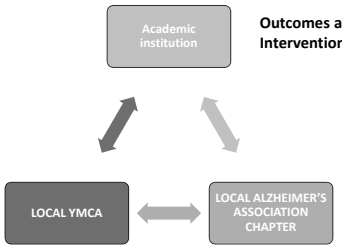
## STUDY DESIGN: COMMUNITY TRANSLATION




36

## STUDY DESIGN: COMMUNITY TRANSLATION

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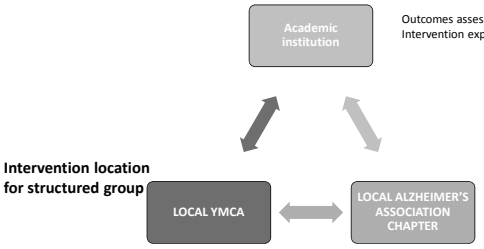
## STUDY DESIGN: COMMUNITY TRANSLATION

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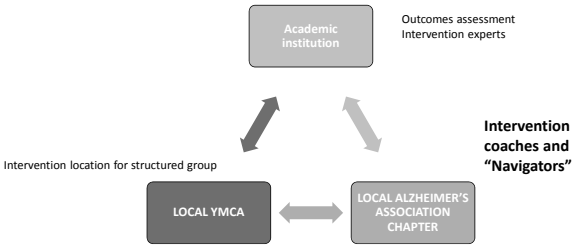


39

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## Participant Contact Schedules

**Self-Guided Group**

| | Timeline | 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' | | | X | | | C | | | X | | | O, Y | | | X | | | C | | | X | | | O, Y, C |

**Structured Group**

| | Timeline | 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 | | | | | | | | | | | | | | | | | | | | | | | |
| | Nutrition[1] | | XXXX | OO | OO | XX OO | XX OO | O | O | O | O | O | O | O | O | O | O | O | O | O | O | O | O | O | O |
| | Cognitive Exercise[1] | | | XXXX | | | | Y | Y | Y | Y | Y | Y, C | Y | Y | Y | Y | C | C | Y | Y | Y | Y | Y | C |
| | Medical Monitoring | | | | XXXX | | | | | | | | | | | | | | | | | | | | |

X = Group Meeting
O = Telephone Call with Dietitian
Y = Health Coaching Appointment
C = Clinic Visits for Outcomes Assessment

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**THANK YOU!**