Prevention Trials for Cognitive loss and Alzheimer's Disease: Finding an invested patient population

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Societal Trends and Dementia

- 65+ age group: fastest growing segment of US population
- Increasing number of elders results in greater incidence and prevalence of AD
- Increasing longevity with disease
- 3- to 5-year period of mild but significant cognitive impairment precedes diagnosis
- Changing technology required for routine activities carries high cognitive demand

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Trials for Prevention: Dementia and Cognitive Loss

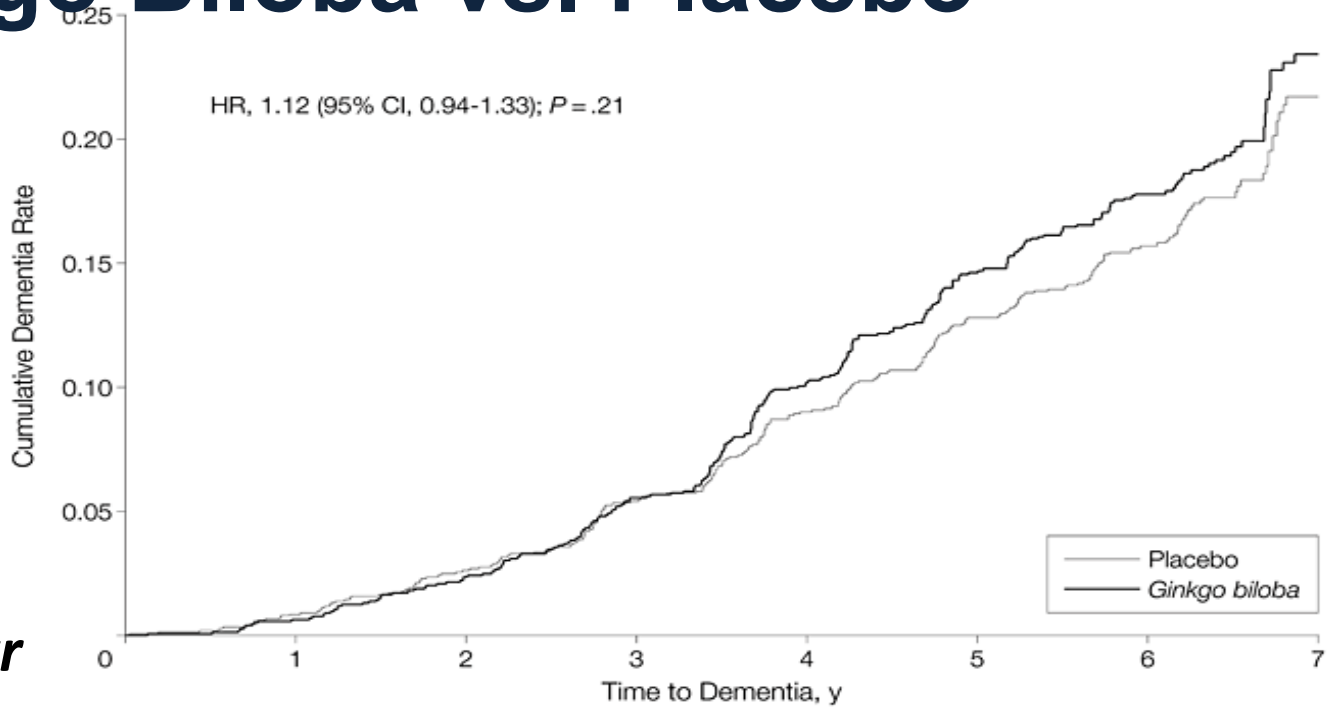
- Dementia Prevention Trials:
  - Large and long
- Prevention of Cognitive loss:
  - Many improve
  - Treatment = greater improvement

Dementia Prevention Trial
Ginkgo Biloba vs. Placebo

>3000 enrolled

With CV risk

7 yrs; <2% change/yr



No. at risk								
Placebo	1524	1485	1423	1342	1243	1148	792	81
G biloba	1545	1521	1458	1369	1254	1129	775	97

No. with incident dementia							
Placebo	13	26	40	50	51	36	30
G biloba	10	26	47	66	60	40	27

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DeKosky, S. T. et al. JAMA 2008;300:2253-2262.

JAMA

Pre-Diva Study

6 year cardiovascular intervention vs usual care trial
Age 70-78

@3500 participants
Risk of dementia: 1%/yr
No effect

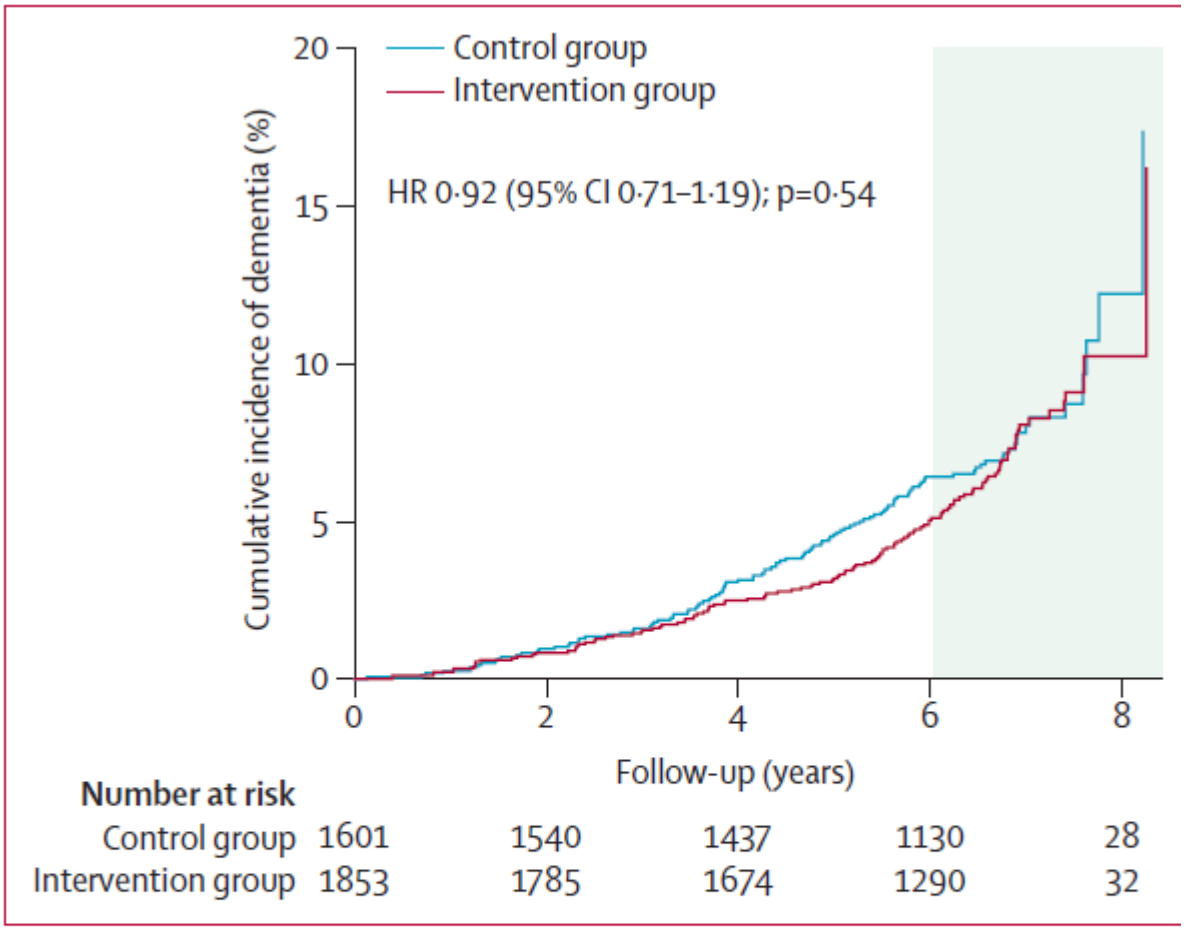

***Figure 2*: Kaplan-Meier plot of cumulative incidence of dementia**
To allow participants recruited early into the trial to continue follow-up until the 6-year assessment of the last participant was completed, the study was extended for participants randomised early (ie, in 2006–07). The hazard ratio (HR) refers to an analysis including all participants, up to 8 years of follow-up. The period beyond the planned 6-year follow-up, concerning few participants, is shaded.

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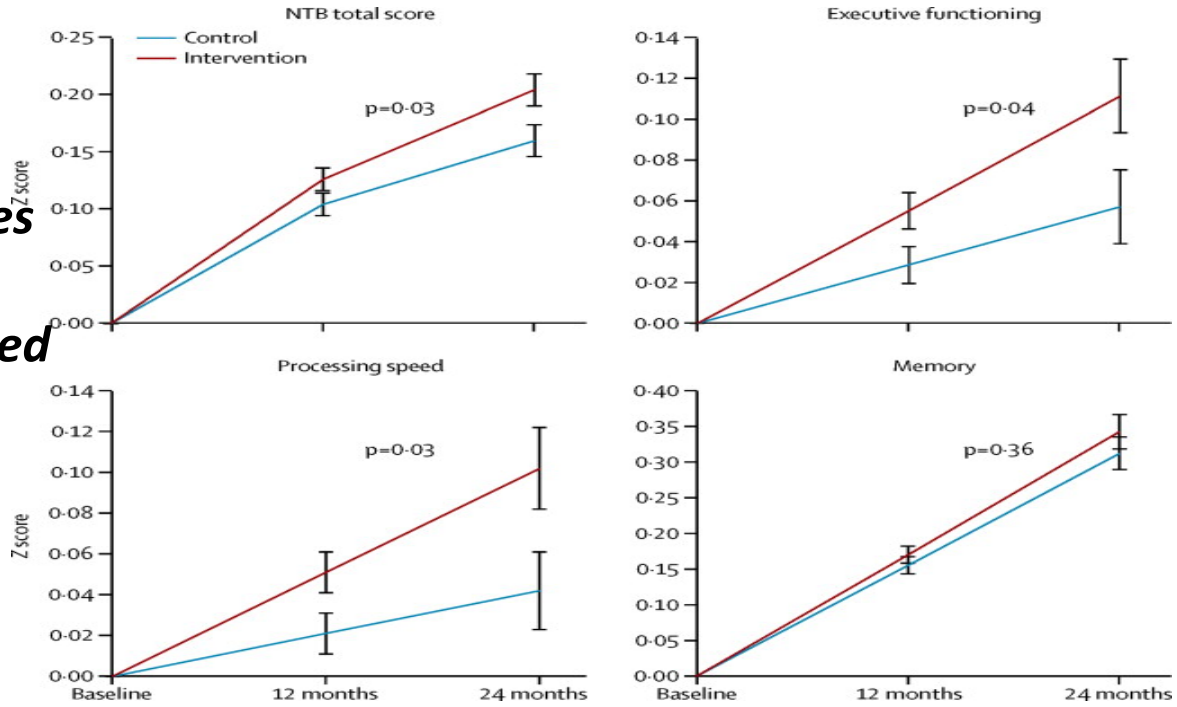
FINGER STUDY RESULTS

Screened 2654 individuals and randomly assigned 1260

Figure 2. Change in cognitive performance during the 2 year interventionFigure shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. E...

Very Small effect sizes

Both groups improved



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

Lancet, Volume 385, Issue 9984, 2015, 2255–2263

Choosing the Right Participants

- Can we select for an “AD like” decline?
- How many do we need?
- How will we engage them?
- What will make them stay?

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Apolipoprotein E for AD Risk

- Risk of AD increased by presence of e4
  - OR=3.2 (95% CI, 2.9–3.5) 1 allele
  - OR=11.6 (95% CI, 8.9–15.4) 2 allele
- Recommendation for use:
  - Only as within clinical work up in symptomatic cases
    - » JAMA 1995
  - Reconsideration in prodromal or non-symptomatic?
    - » Alzheimer &Dementia 2011

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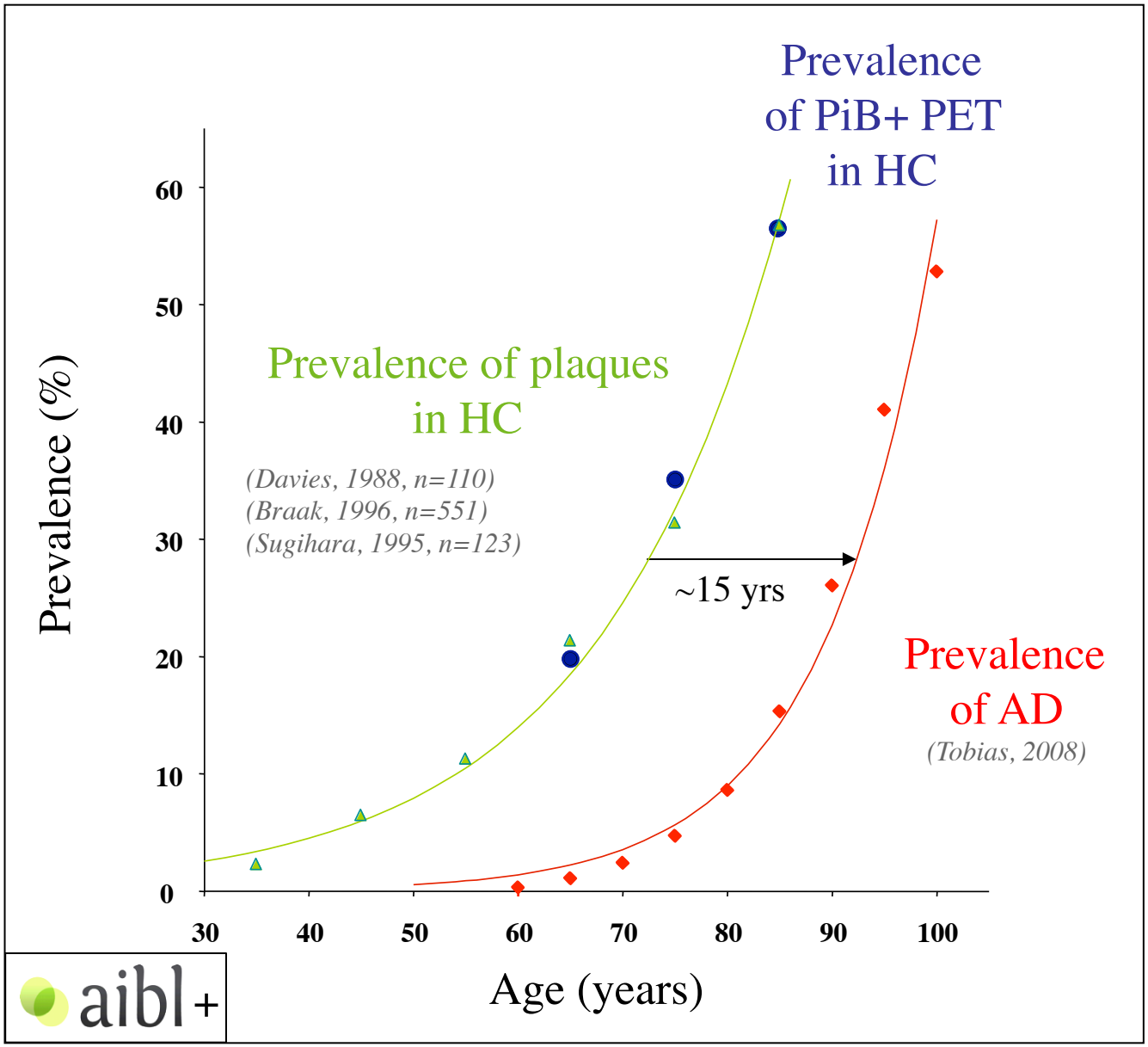
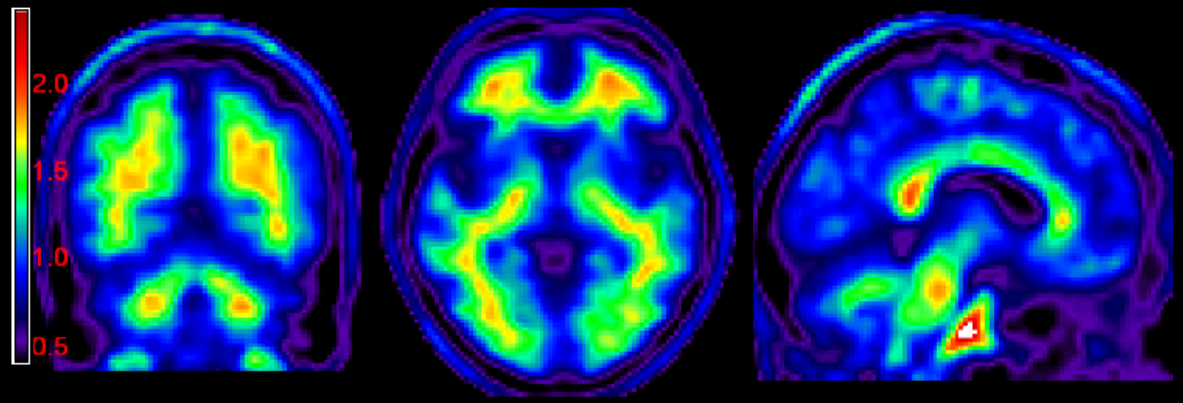
Preclinical Alzheimer's Disease?

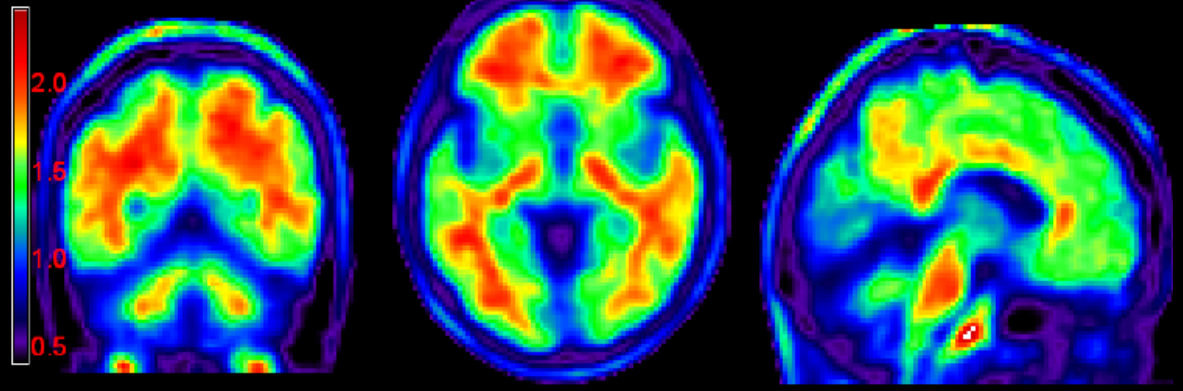


^{18}F-AV-45 Representative Images: Healthy Controls

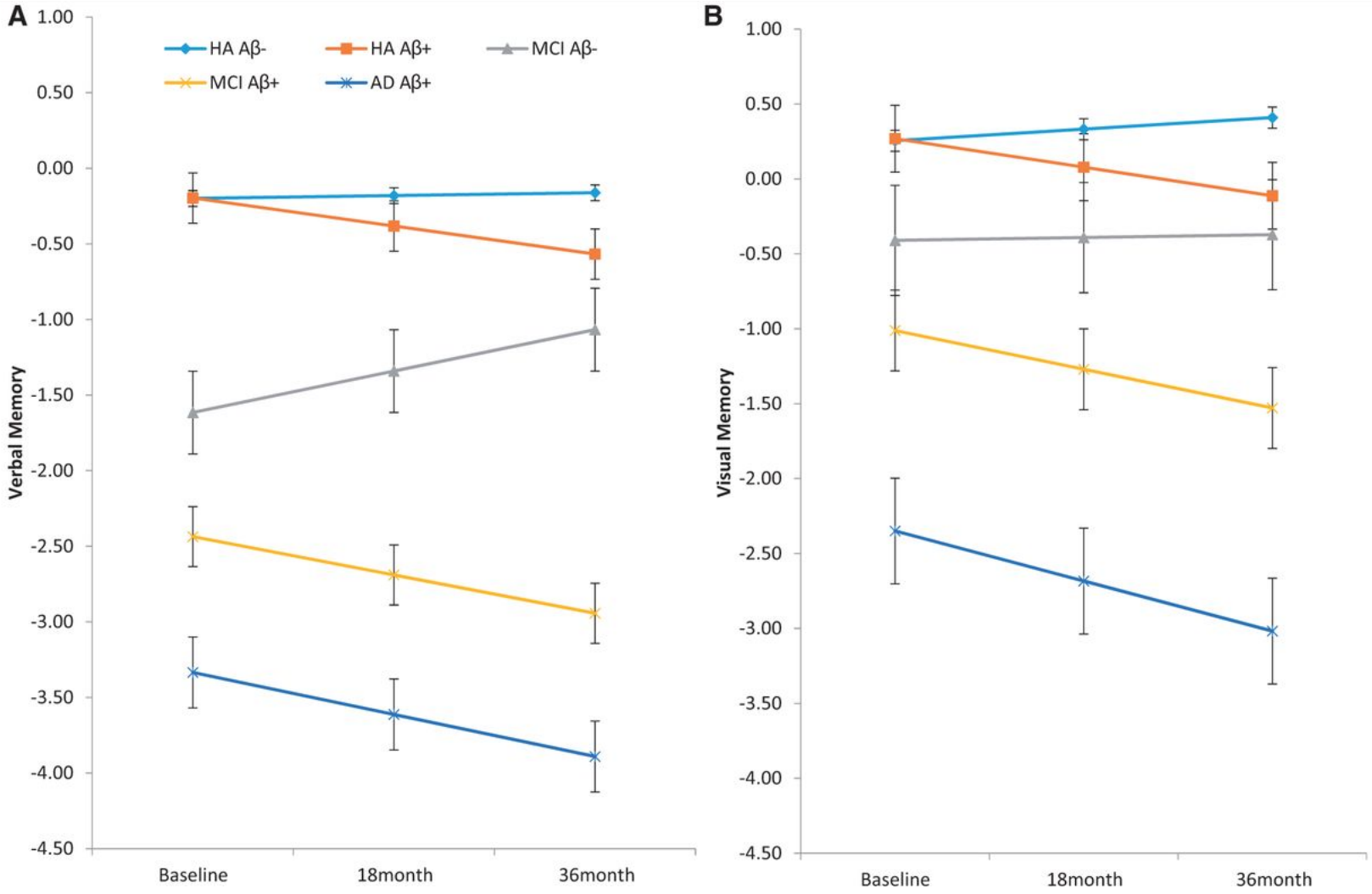
Amyloid Negative HC



Amyloid Positive HC



Effect of amyloid
Decline in cognition over time



AIBL data

Challenges

- Disease modifying agents: benefit unlikely to be observable by patient
- Disease prevention vs. Clinical improvement
  - Unique/different populations require different recruitment and intervention strategies
- Technologies have a place but do not replace human touch
- Success or lack of it is not a secret and needs to be integrated into recruitment and retention strategies

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Recruiting from Clinical Practice

- Perception of clinical population often overestimates recruitment
- Why?
  - Clinical bond may be a strong motivator for subject participation
  - Balance of “bond” and “bother”
  - Focus on inclusion criteria NOT exclusion criteria

Why True Eligible and Perceived Eligible Differs

- Commitment to experimental approach may not be high
- Procedures for standardization may have little clinical relevance to volunteers
- Concept of placebo is complex and not readily accepted by participants and families
- Adverse effect may be higher than recognized

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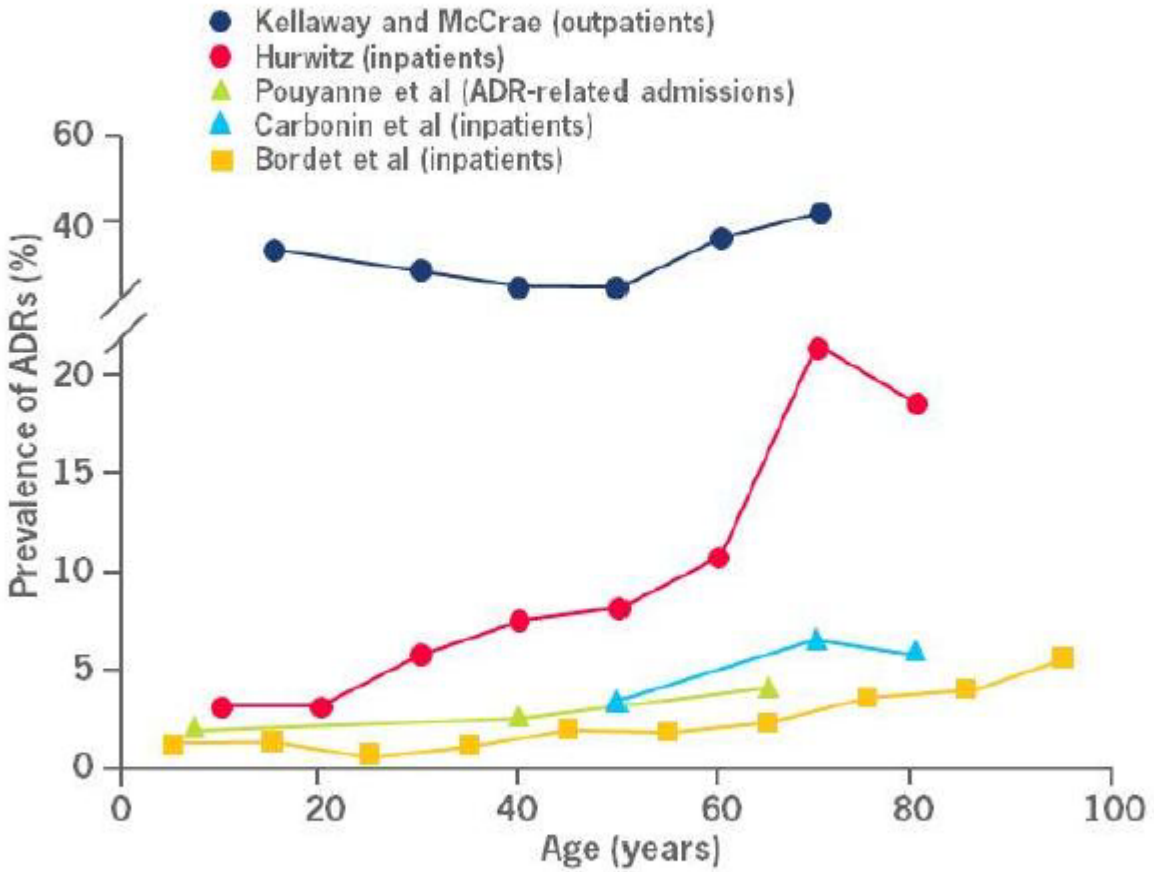
Vulnerability: Relationship between Age and Adverse Drug Reactions



Source: McLean, LeCouteur. "Aging biology and geriatric clinical pharmacology." *Pharmacol* Rev 2004 Jun;56(2):163-84.

Overview

- Three studies
  - How do we select our message
    - Decision Making for brain donation
  - Retention
    - Why do they stay
  - Addressing burden with Home based assessment
    - Research satisfaction

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Decision-Making Concerning Brain Donation in Alzheimer's Research Among Research Participants and Their Families

Sewell M, Neugroschl J, Li C, Sano M.

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Background

- **To improve low rate of interest in brain donation**
- **N=97 (65 participants and 32 study partners)**
- **Previously declined or were unsure**
- **Open--ended questions about being approached**
  - **personal & general feelings about brain donation for research.**
- **Responses were qualitatively evaluated**
  - **Could be coded in > 1 category.**
- **Result:**
  - **23% changed their status from "undecided" to "yes"**
  - **(25% of participants and 19% of study partners.)**

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Reluctance and Concerns

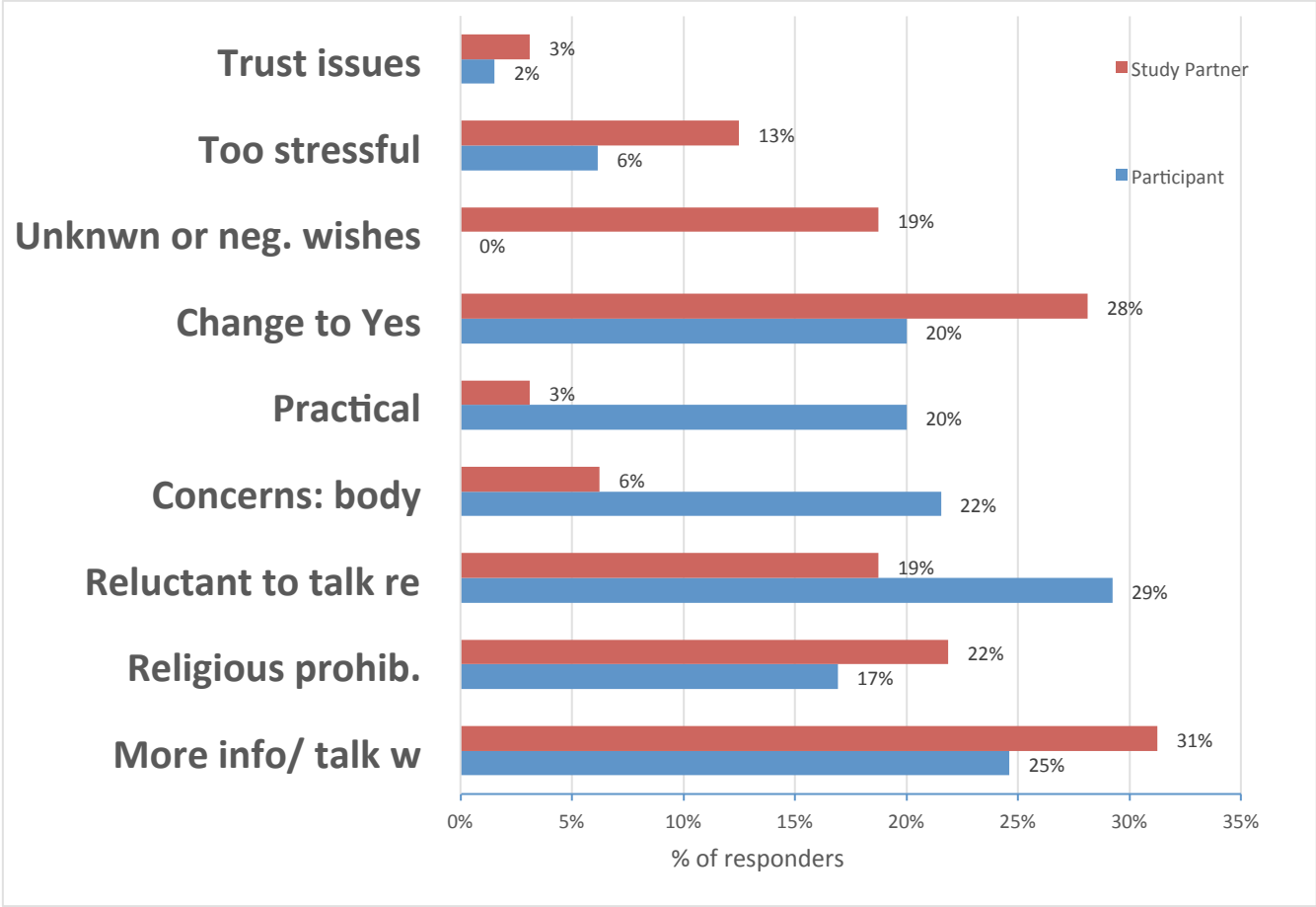
Type of response	# Resp	P/SP	Sample responses:
Need more information to share and talk with family	26	P 16 SP 10	"I want to discuss it with my daughter." "Tell me more about the process." "I need to speak to my doctor and family members."
Religious prohibition	18	P 11 SP 7	"I'm Jewish. The body is not supposed to be anything but whole." "I don't believe in it for religious reasons."
Reluctance to talk about death	25	P 19 SP 6	"....it's not a pleasant conversation." "The thought of dying is hard." "I'm healthy; I'm not ready to make a decision." "....very overwhelming to think about it…."
Concerns about body integrity	16	P 14 SP 2	"I might need it." "…I understand the benefits, but I don't want my body altered." "I want to die with everything I have…."
Practical concerns	14	P 13 SP 1	"How is it done? Will they drain my brain?" "How will you know that I have passed away?" "What if I'm not local?"

Similar

Conviction and Decision

Type of response	# Resp	P/SP	Sample responses:
Planning on changing decision from no/ undecided to "Yes"	22	P 13 SP 9	"Ready to sign up!" "It will help my family ….know if my father really has AD." "…We want to help future patients." "I won't be using my brain anyway after I die, so why not donate..'
Unknown or known negative wishes of the participant	6	P 0 SP 6	"My mother was …unlikely to donate when she was lucid." "I never discussed it with my dad … feel he would have said yes…but since he cannot express his wishes I cannot make this decision for him."
Too stressful	8	P 4 SP 4	"I just can't see the point--it won't help her. I just don't want to put her--and I suppose myself--through that." "… unnecessary grief for my children during an already tough time."
Trust issues	2	P 1 SP 1	"If I were ever hospitalized and there was a complication, would they harvest my brain before my time was up?" "I'm concerned how well the brain will be used."

What Drives the Decision



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Why They Stay: Understanding Research Participant Retention in Studies of Aging, Cognitive Impairment and Dementia

Judith Neugroschl[1], **Mary Sano**[1,2], **Xiaodong Luo**[1], and **Margaret Sewell**[1,*]

53 Participant

- **33 participants**
- **20 Study Partners**

2 or more visits to the center

"We are interested in identifying reasons why research volunteers like you choose to continue participation over time....
can you tell us your main reason(s) for staying?

Voices and Categories

Personally empowering	**“Helps me take control of this**
Obligation	**“My wife makes me.” “I made a commitment to [my doctor].”**
Financial	**“It’s free care.” “Being paid is a perk.”**
Value to my family	**“(AD) runs in my family, so maybe this means my children will be free ”**
Altruism	**“I want to help defeat the terrible problem of AD.” “If I can help, why not?” “Gives me pride to**

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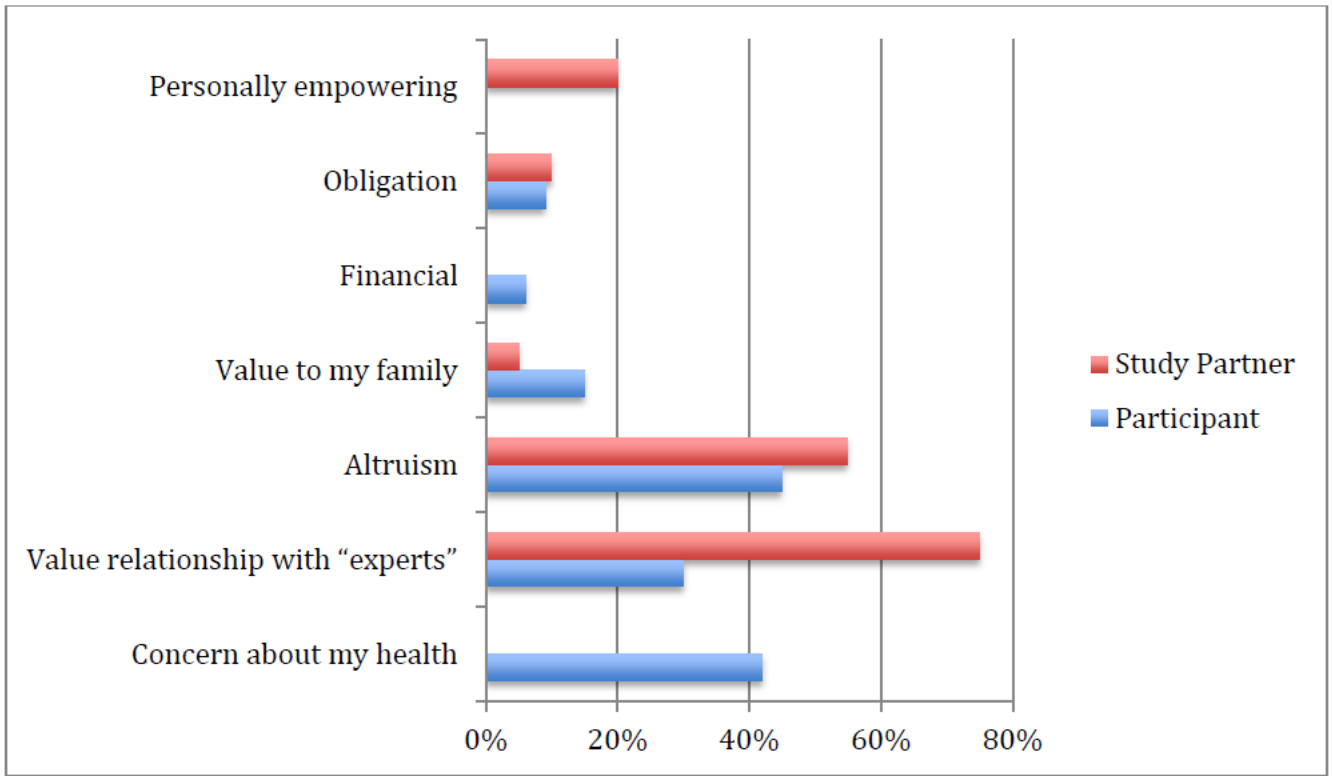
Study Partner and Participant responses in each category



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Challenges to recruiting for "Prevention"

- Messaging:
  - Convey the need to do the research (risk/fear)
  - Engage and empower people (ego?)
  - Inform of science &commitment (burden)
  - Maintain and retain (reinforcing)
- Listening:
  - What is the understanding
  - What is the perceived benefit
  - What is experienced burden

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Assessing Clinical progression for Dementia Prevention Trials: Results from the HBA trial

Mary Sano

Susan Egelko, Michael C Donohue, Jeffrey Kaye, James Mundt, Chung-Kai Sun, Steven Ferris, Paul S. Aisen,

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Home Based Assessment (HBA) trial

- Designed to develop efficient/effective methods for in-home evaluation
- Random assignment to 1of 3 arms

Mail-in & Live Phone
MIP

Interactive Voice Response
IVR

Computer Kiosk
MIP

Study Features

- Randomized study conducted at 27 site
- 581 non-demented participants completed in-person assessment and baseline HBA
- Assessed with brief instruments from domains important to transition to dementia
  - -- Cognitive -- Functional
  - -- Global -- Behavioral
  - -- QOL -- Pharmacoeconomic
- 4 Yr Follow up; face to face at start and end

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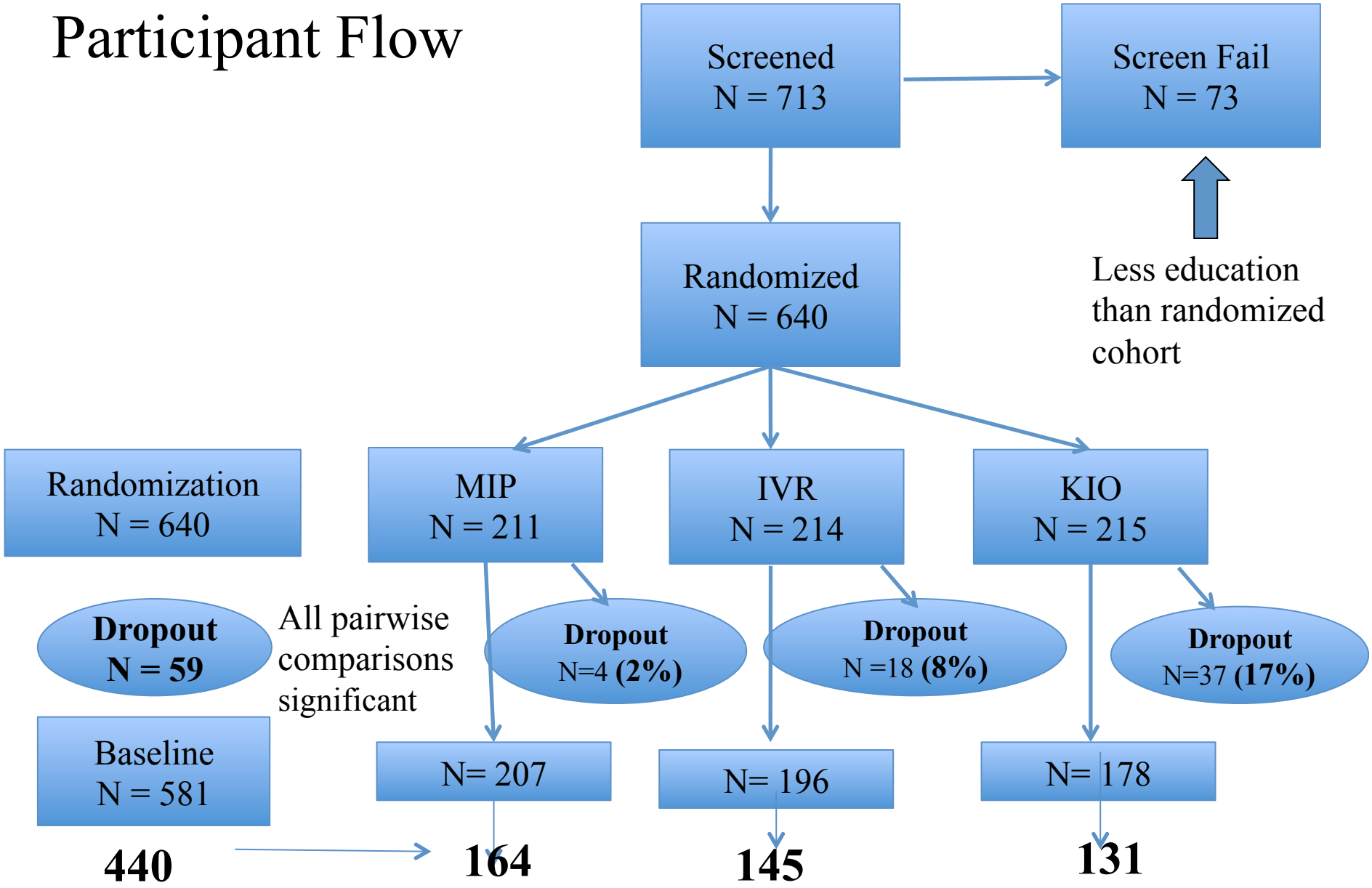
Participant Flow



Demographic and Clinical Characteristics of Baseline Cohort: All Arms Combined

N	581
Age *	80.9 (4.4) Range = 75 – 98
Education	15.6 (2.9) Range = 0 – 20
% Female	67
% Racial/ethnic minority *	22
% Married	42
% History of hypertension	59
% Cardiovascular disease	74

No differences between baseline cohort and cohort that passed screening and discontinued after randomization

Who Refused and Why?

Drop Out By Arm And Frequency		
MIP Annual	4 /105	4%
MIP Quarterly	0/106	0%
IVR Annual	7/107	6%
IVR Quarterly	11/107	10%
KIO Quarterly	16/109	15%
KIO Monthly	21/106	20%

Nature of complaints:

Inconvenience of the equipment

Too much time to participate

Dissatisfaction with Technologies

- **“so ugly”**
- **“takes up so much room”**
- **“glow disturbs sleep”**

- **“interference of phone line”**
- **“static on line”**

Stemming the Tide

- Drop out continued
- Research Satisfaction Survey at 18 mo into enrollment
- 8-item survey
- Open ended questions about preferences

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Survey results

- Overall high satisfaction
- Highest among the low technology (MIP)
- Lowest among IVR

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"The thing I have liked best about my experience in the study is . . ."			
Rank	**#**	**%**	**Category**
1	**60**	**18.3**	**volunteerism; contribute to AD research**
2	**58**	**17.7**	**challenged to improve own mental functional**
3	**55**	**16.8**	**positive interactions with study personnel**
4	**47**	**14.4**	**feedback on own mental functioning, whether reassuring or pointing to difficulties**
5	**30**	**9.2**	**fun, easy, filled time, interesting, engaging, liked test-taking in general, mental activity**
6	**26**	**8.0**	**education; increased awareness of what types of tasks are difficult with Alzheimer's Disease and/or aging**
7	**18**	**5.5**	**convenience of being tested at home; no driving involved**
8	**15**	**4.6**	**limited time commitment, either in frequency or length of testing**
15	**6**	**1.8**	***nothing* mentioned regarding what was liked most**

mCSQ-8 Open-Ended Question #2: “What I liked least was . . .			
Rank	Count	%	Category
1	87	29.3	nothing
2	43	14.5	objected to particular tests: repeating numbers backwards & story recall; finding tests “boring”
3.5	22	7.4	repetitiveness of each visit; some questioning validity, citing how much retained from prior visit
3.5	22	7.4	feeling inadequate, not liking being tested, nervous, aware that memory not what it once was
5.5	15	5.1	amount of time it took, especially if on a busy day

What would you change….

Rank	#	%	Category
1	104	39.4	*nothing* to change
2	34	12.9	change test items, eg., have alternate form
3	12	4.5	more personal contact with staff or fellow seniors
4	11	4.2	give us feedback, instruct us on how to improve our memory
5	9	3.4	change specific tests that are not enjoyed (story recall, #s backwards)
8	7	2.7	change the avatar (computer and audio tester), experienced as overly stern
8	7	2.7	improve the technical aspect of equipment used, eg, size, ugliness, etc.
8	7	2.7	allow testee to fastforward through listening to their own baseline account of their level of functioning (CGI)
8	7	2.7	change aspects of the vitamin-taking
8	7	2.7	improve flaws specific to the KIO operating system, requiring maintenance visits for breakdowns

Comparing Technologies

- No complaints:
  - MIP arm 48%
  - IVR arm 27 %
  - KIO arm15%
- Dislike of arm specific procedures:
  - KIO arm 35%,
  - IVR arm 8%
  - MIP arm4%

Estimating Yield
Lessons from SPRINT

Ramsey et al 2016

Greater than or Equal 75				
Source	# Screened	# Randomized	Ratio	% of total
Mass Mail	1726	1194	69%	44%
Media	203	116	57	4%
Staff Referrals	1402	1036	74%	38%
Brochures	608	395	65%	15%
Total	3756	2636	70	100%

LESS THAN 75				
Source	# Screened	# Randomized	Ratio	% of total
Mass Mail	3098	1808	58.4	27
Media	1041	584	56.1	7
Staff Referrals	5145	3450	67.1	51
Brochures	1584	921	58.1	13
Total	10,692	6725	61.1	100%

Older cohort accurately identified by referral; but less likely to be referred

Older cohort 57% less likely to be recruited from media

Conclusions and Considerations

- Participation is driven by many things, but mostly altruism
- Hesitation is driven by lack of information, understanding or conviction of value
- Sometimes no is no
  - Religious and cultural beliefs, and experience are strong and may be immutable …. Move on!

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Conclusions and Considerations

- Retention is about delivering
- Clear preference for interpersonal over technology
  - Staff
  - Requests to meet others
- Asking about satisfaction improves participation
- Asking before we begin may be even better

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Why Clinical Research Participations ?

Clinicians

- Low referrals, delay new diagnostics, and treatments
- Mutual referral relationships
  - Tertiary care research centers need referral options
  - Enhance practice credibility

Patients

- Standardized evaluations as baseline
- Access to up-to-date research initiatives
- Potential for earliest access to medications
- Support for family and friends
- Contribution from self to family, society***

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Whose job to support research

- Clinicians
  - Know how to refer to research,
- Volunteers (w or w/o disease)
  - Discuss with your family
  - Support the decision, be a study partner
- Everyone
  - Support public funding
  - Make your contribution

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Not all studies for all participants

- Inclusion criteria:
  - Insure safety
  - Limitations by age co-morbidities other medications
  - Insure the ability to measure efficacy
  - Hearing / visual difficulties make
- How to Choose:
  - Select by interest
  - Work with those you trust
  - Be honest about how much you can do
  - Ask questions

Remember, you can always change your mind

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