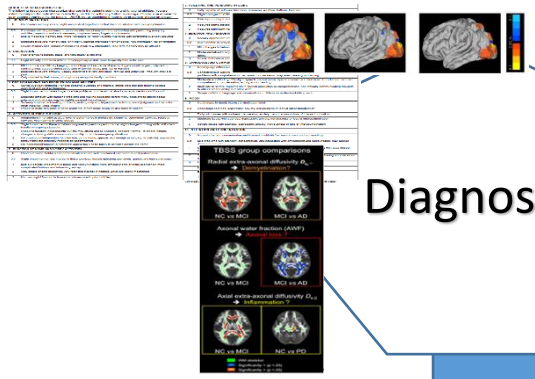
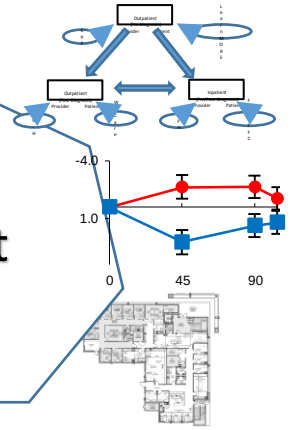


Diagnose



Treat

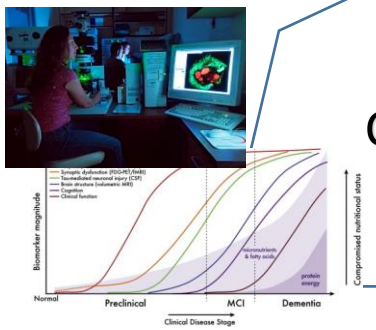
Advances in Alzheimer's Disease

James E. Galvin, MD, MPH

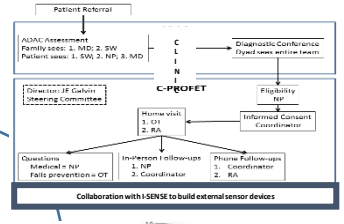
Professor and Associate Dean for Clinical Research

Director, Comprehensive Center for Brain Health

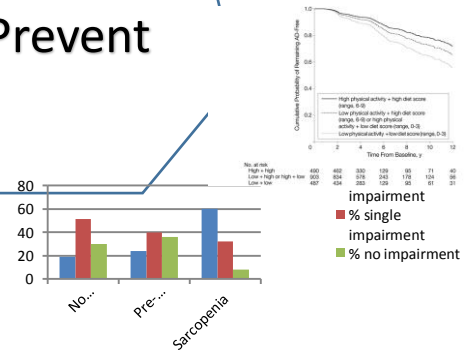
Director, Institute for Healthy Aging and Lifespan Studies



Cure



Prevent



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- Consultant
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What is healthy brain aging?

- The absence of cognitive decline
    - Occurs into the 10th decade of life
    - Still carry out their activities of daily living
    - Lead a productive and happy life

- With age, it may take longer to do things or recall information, but it usually comes back

- Memory loss is **not** a normal part of the aging process

What is Dementia?

- A general word to describe:
  - Change in memory and thinking abilities
  - Interferes with everyday function
  - Not caused by another disease
- Not really a diagnosis
- There are over 100 different causes of dementia

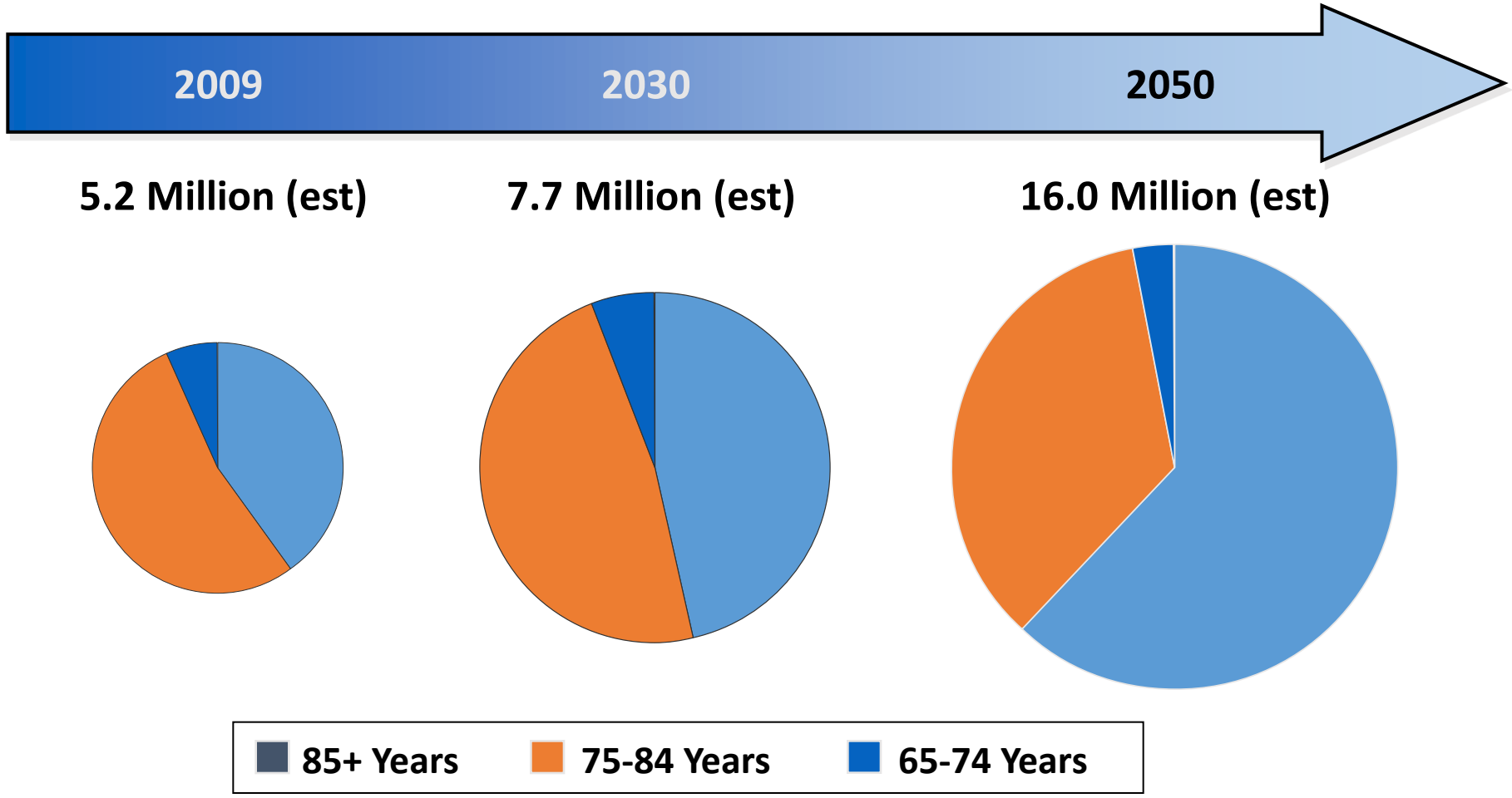
What is Alzheimer's Disease (AD)?

- Most common cause of dementia
- 5.4 million Americans have AD
  - 250,000 age <65 years (early-onset)

AD Prevalence by Age in Adults ≥65 Years		
Age (y)	**Proportion**	**Number**
65-74	2%	300,000
75-84	19%	2,400,000
≥85	42%	2,200,000

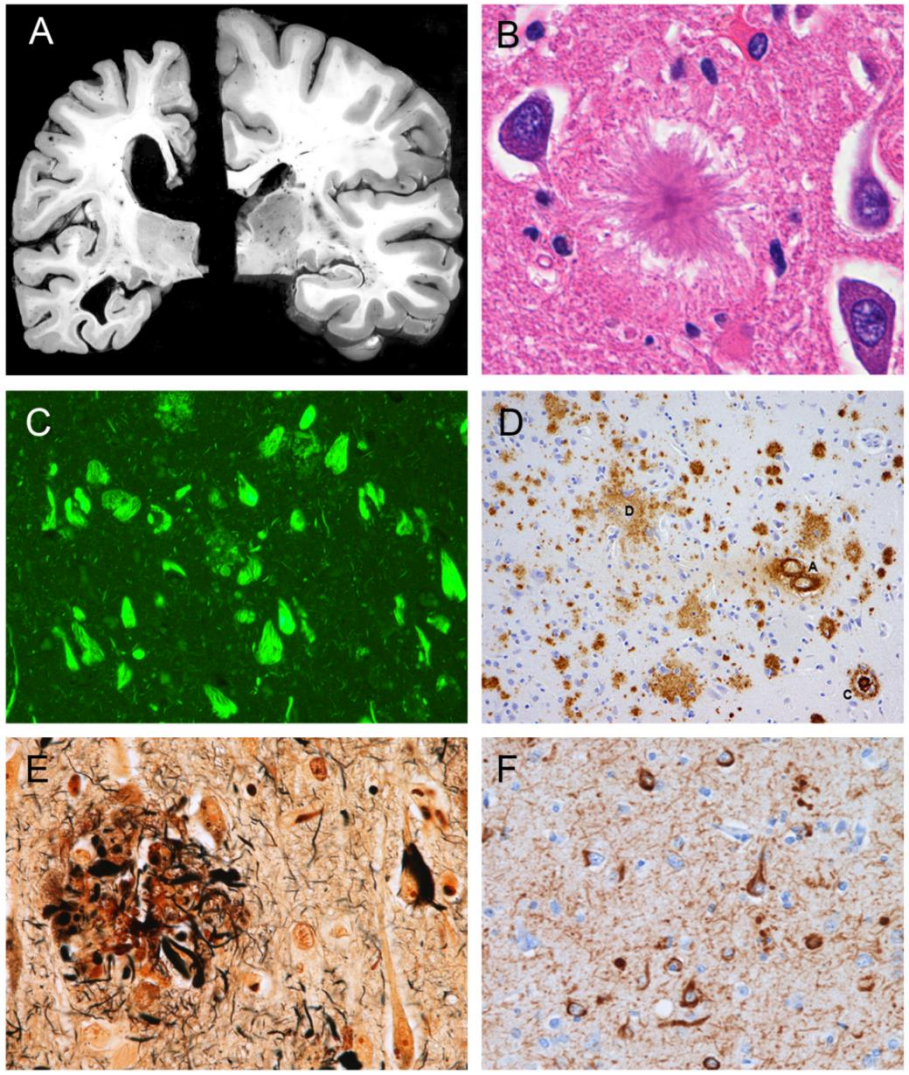
- Annual treatment costs > $200 billion
  - Costs increase as disease progresses
  - 3rd most expensive disease after cardiovascular and cancer
- Sixth leading cause of death in the US (over age 70)
- Makes up 50% of all nursing home beds
  - Median cost (2013) = $84,000

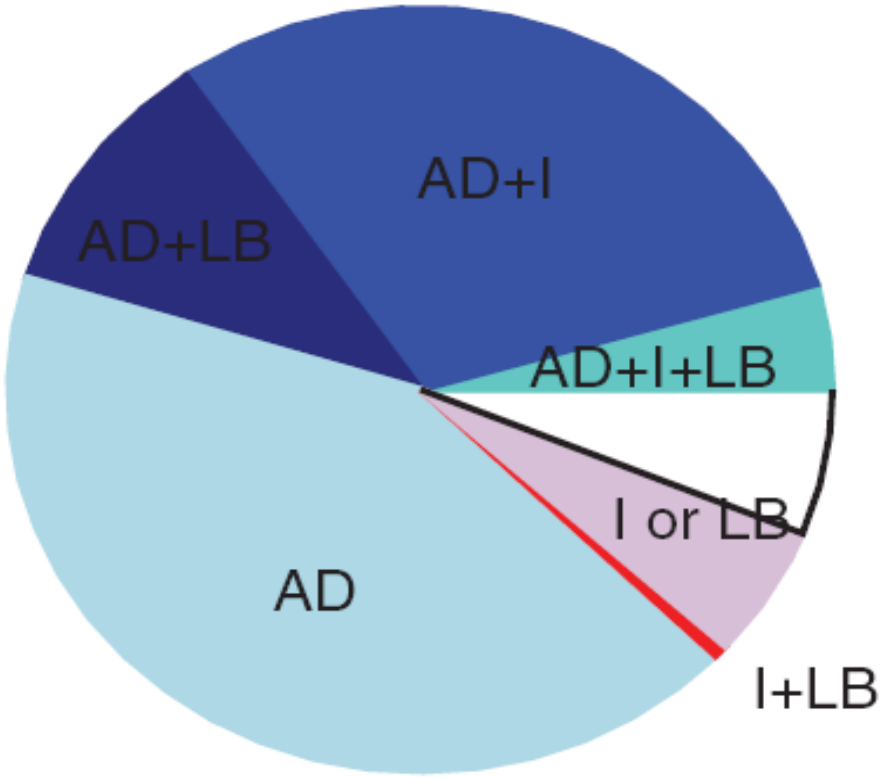
Forecast of Alzheimer's Disease Prevalence



1. Hebert LE, et al. *Arch Neurol*. 2003;60(8):1119-1122.
2. Alzheimer's Association. Alzheimer's Disease Facts and Figures: 2009.

The Neuropathology of AD



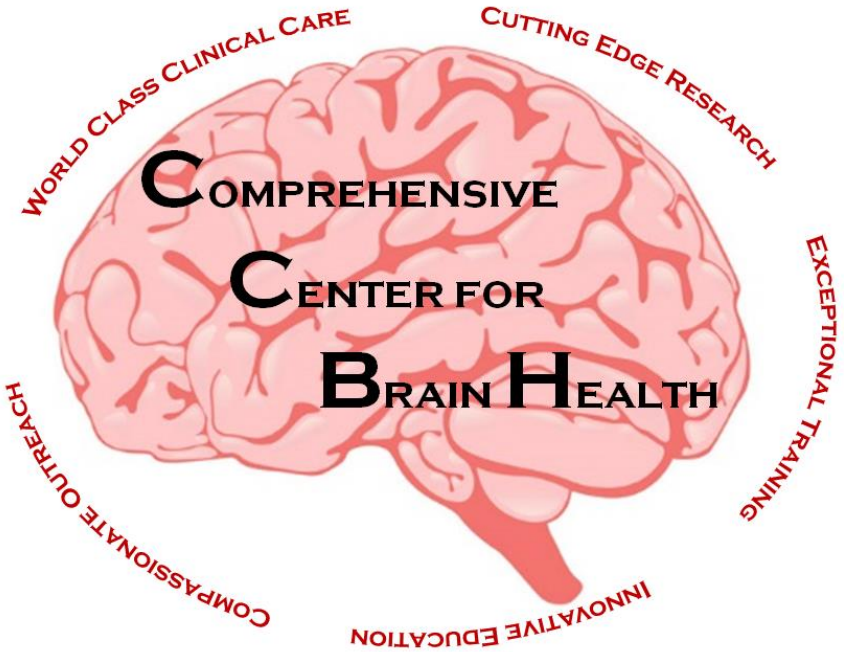


Mixed pathology is most common cause of the clinical picture of AD.

AD: Alzheimer disease
I: Vascular disease
LB: Lewy body disease

Comprehensive Center for Brain Health

- Center of Excellence devoted to world-class comprehensive clinical care and cutting-edge research advances
- Prevention, treatment and cure of neurodegenerative diseases
- Expertise in:
  - Healthy brain aging and Prevention Services
  - Alzheimer's Disease and cognitive disorders
  - Parkinson's Disease and movement disorders
  - Therapy, counseling, and rehabilitative services
  - State of the art brain imaging and mapping
  - Basic and Translational Science Laboratories
- Translate basic, clinical, behavioral and social research into innovative programs and practices that improve health outcomes and reduce health disparities

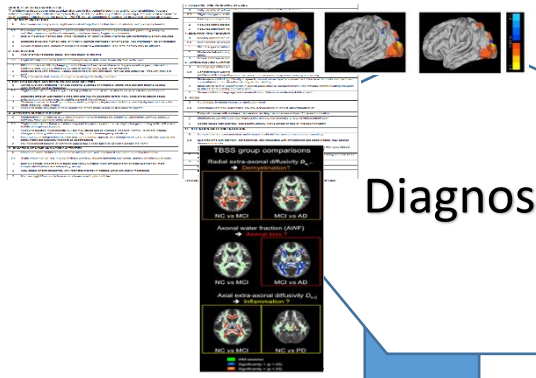


Chronic Diseases in South Florida

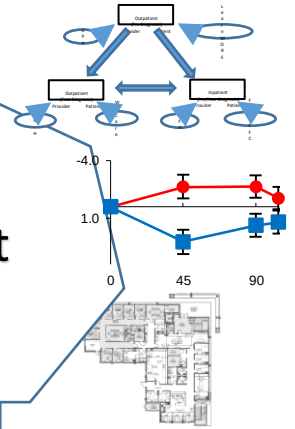
Prevalence of Chronic Disease in Medicare Beneficiaries (2013 Data)				
	National	**Florida**	**Palm Beach County**	**Broward County**
Beneficiaries	34,126,305	2,243,566	174,150	119,379
Mean Age, y	71	73	75	73
Gender, % Female	55.1	54.7	56.2	55.8
Dual-eligible, %	21.7	19.3	11.2	23.9
Alzheimer's Disease[1] (%)	**9.8**	**11.3**	**11.5**	**12.7**
Depression (%)	15.4	16.4	15.2	17.9
Coronary Heart Disease (%)	28.5	37.1	42.7	37.8
Diabetes (%)	27.0	28.5	28.9	29.1
COPD (%)	11.9	13.6	9.7	12.4
Hypertension (%)	55.5	60.8	60.3	58.8
Hypercholesterolemia (%)	44.7	55.5	60.2	52.9
Strokes (%)	3.8	4.5	4.6	4.8
[1]Includes related dementias				

Aging and Dementia Research Program

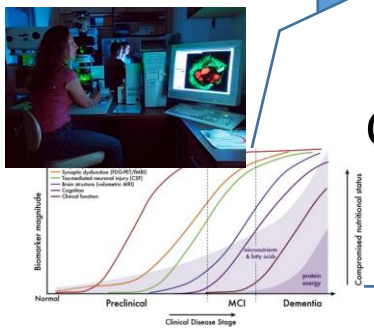
Diagnose



Treat



Cure



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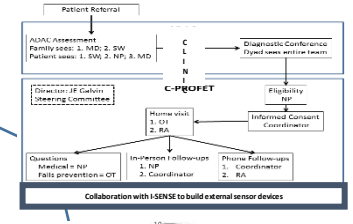
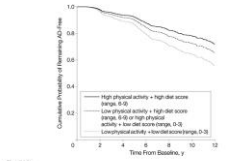
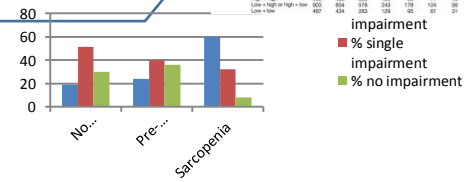






The AD8

Interview (either informant or patient)

- 2-3 minutes to complete
- In-person, phone, or web

Remember, "Yes, a change" indicates that you think there has been a change in the last several years cause by cognitive (thinking and memory) problems	**YES**, A change	**NO**, No change	**N/A**, Don't know
Problems with judgment (e.g. falls for scams, bad financial decisions, buys gifts inappropriate for recipients)			
Reduced interest in hobbies/activities			
Repeats questions, stories or statements			
Trouble learning how to use a tool, appliance or gadget (e.g. VCR, computer, microwave, remote control)			
Forgets correct month or year			
Difficulty handling complicated financial affairs (e.g. balancing checkbook, income taxes, paying bills)			
Difficulty remembering appointments			
Daily problems with thinking and/or memory			
TOTAL AD8 SCORE			

- Report cognitive loss in comparison with patient's premorbid function
- Report interference with usual daily activities
- Consistent change, even when patient's brief test performance is "normal", may detect earliest symptomatic stages of dementia
- Less biased by race, culture, education or SES
- Dependent on a reliable, observant informant

Galvin JE et al, Neurology, 2005

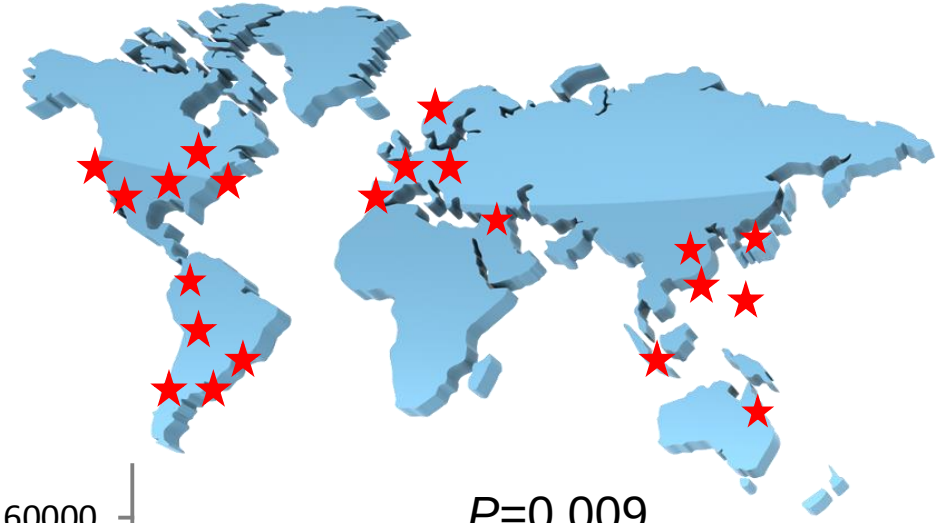
The AD8

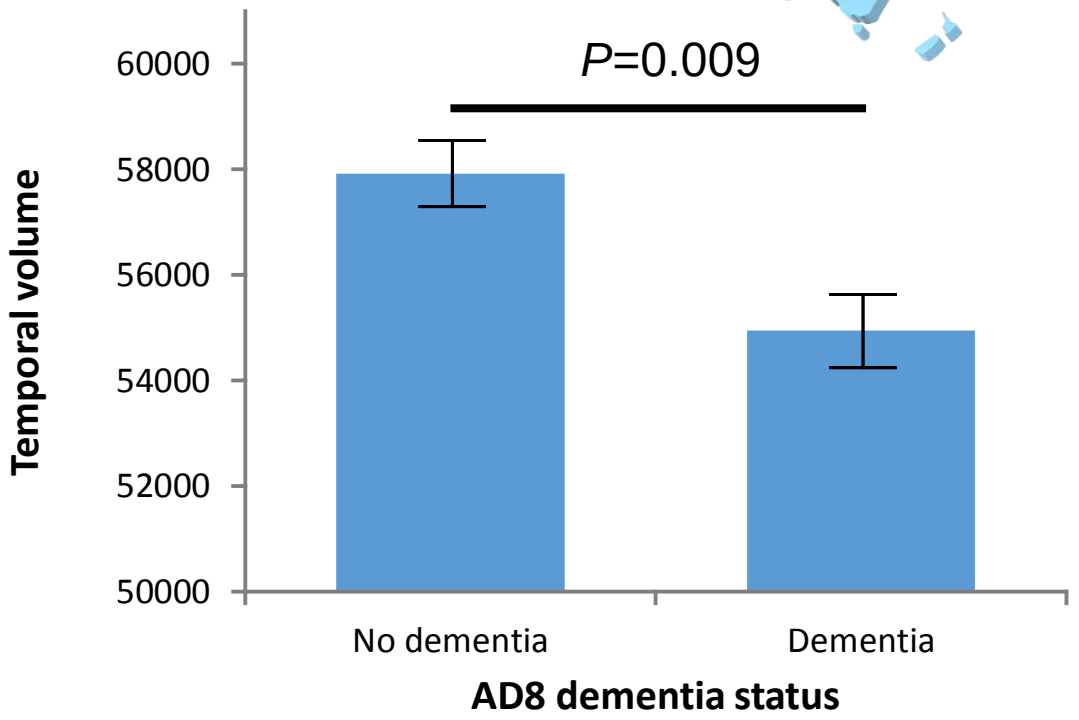
		Mean AD8 score (± SD)	
CDR	**N**	**Informant**	**Patient**
0	149	0.64 (1.19)	1.01 (1.52)
0.5	102	3.49 (2.32)	2.80 (2.19)
Cohen's d		1.66	0.98

Variable	AD8 < 2	AD8 ≥ 2	*P*
Demographics			
Age, years	75.3 (7.2)	75.5 (7.5)	ns
ApoE, % ε4	30.1	48.7	.003
Dementia Ratings			
CDR-SB, range 0-18	0.06 (0.19)	2.8 (2.5)	<0.001
AD8, range 0-8	0.3 (0.5)	5.0 (2.1)	<0.001
MMSE, range 30-0	28.5 (1.5)	25.8 (4.6)	<0.001
Biomarker Studies			
PiB Amyloid, units	0.12 (.23)	0.45 (.42)	<0.001
CSF Ab_{42}, pg/ml	590.7 (266.2)	435.6 (209.6)	<0.001
CSF tau, pg/ml	303.6 (171.2)	500.5 (261.3)	<0.001
CSF p-tau_{181}, pg/ml	52.2 (23.9)	76.7 (39.9)	<0.001

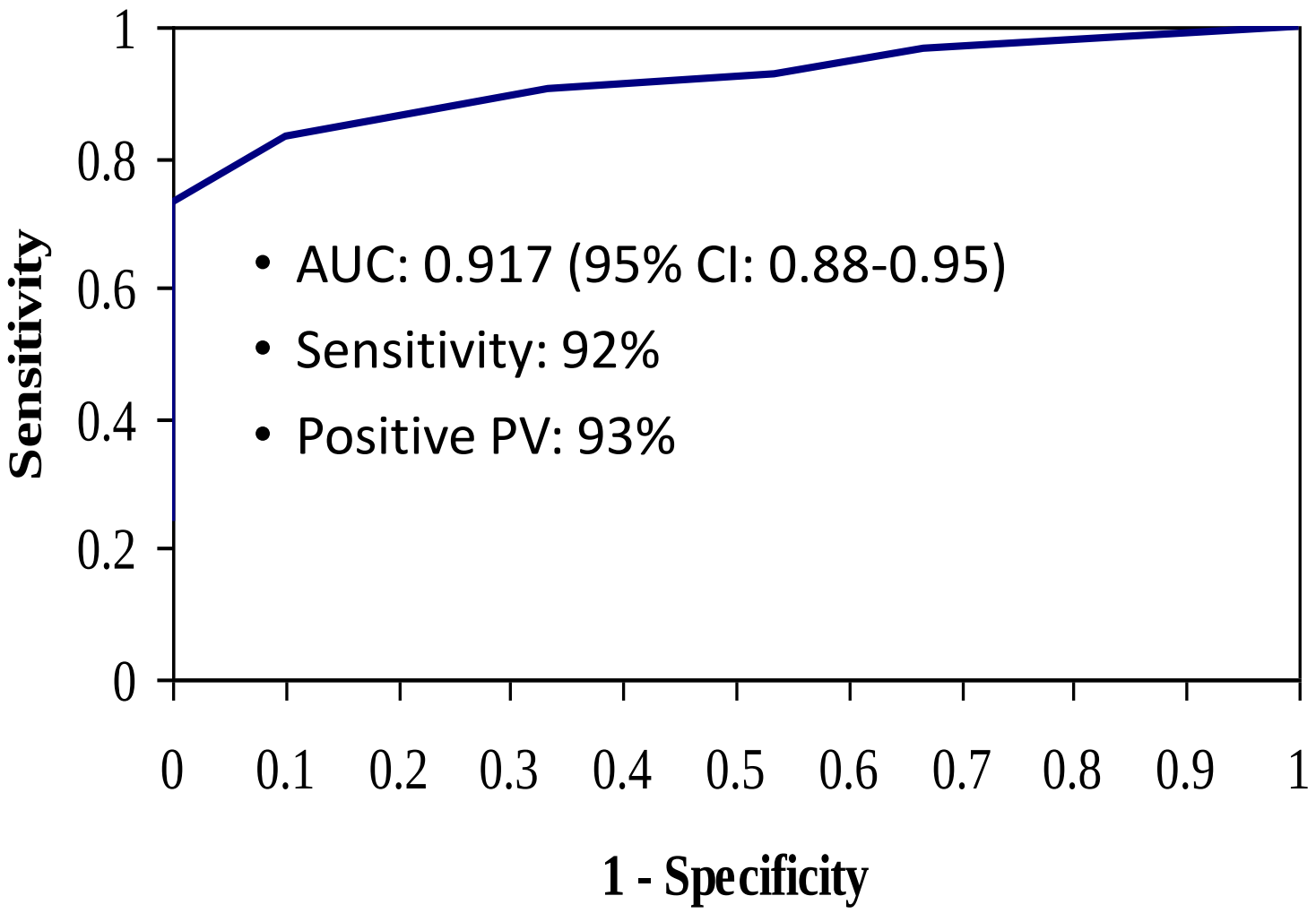
Galvin JE et al., *JAMA Neurol* 2007; 64:725-730; Galvin JE et al., *Brain* 2010;133:3290-300

- Works across cultures/languages





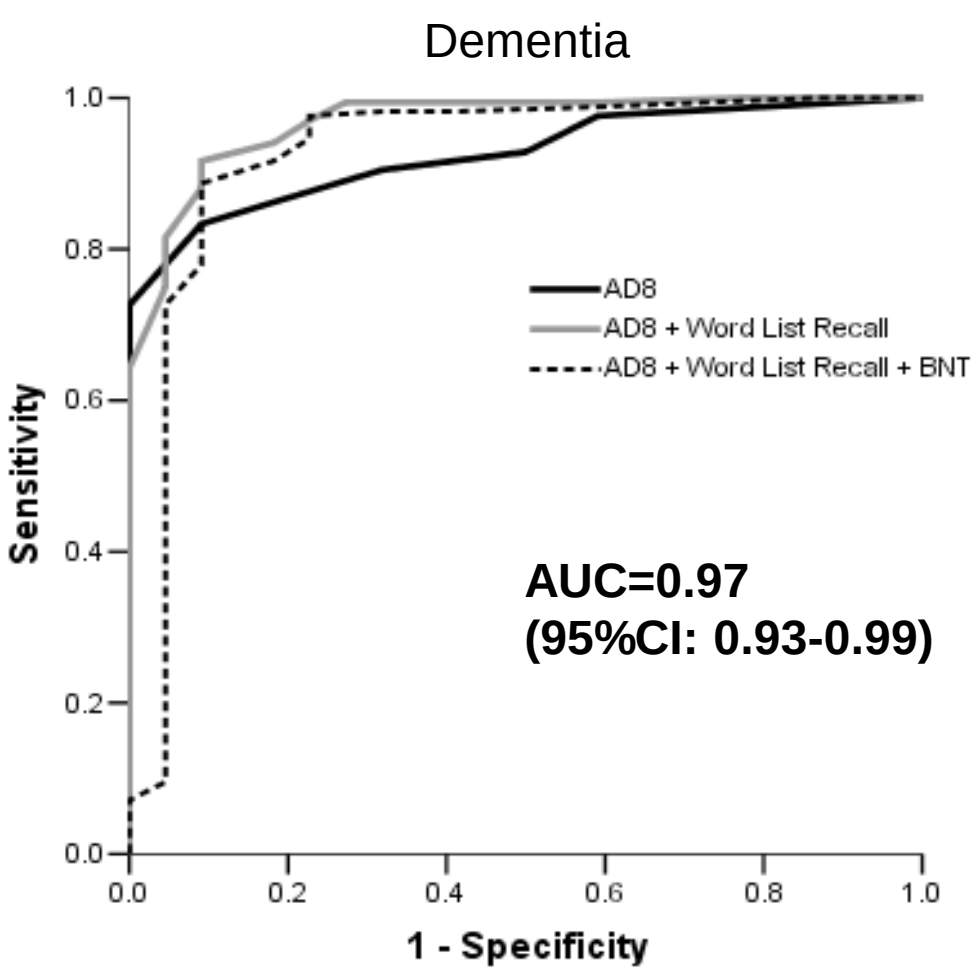
AD8 Discriminative Properties

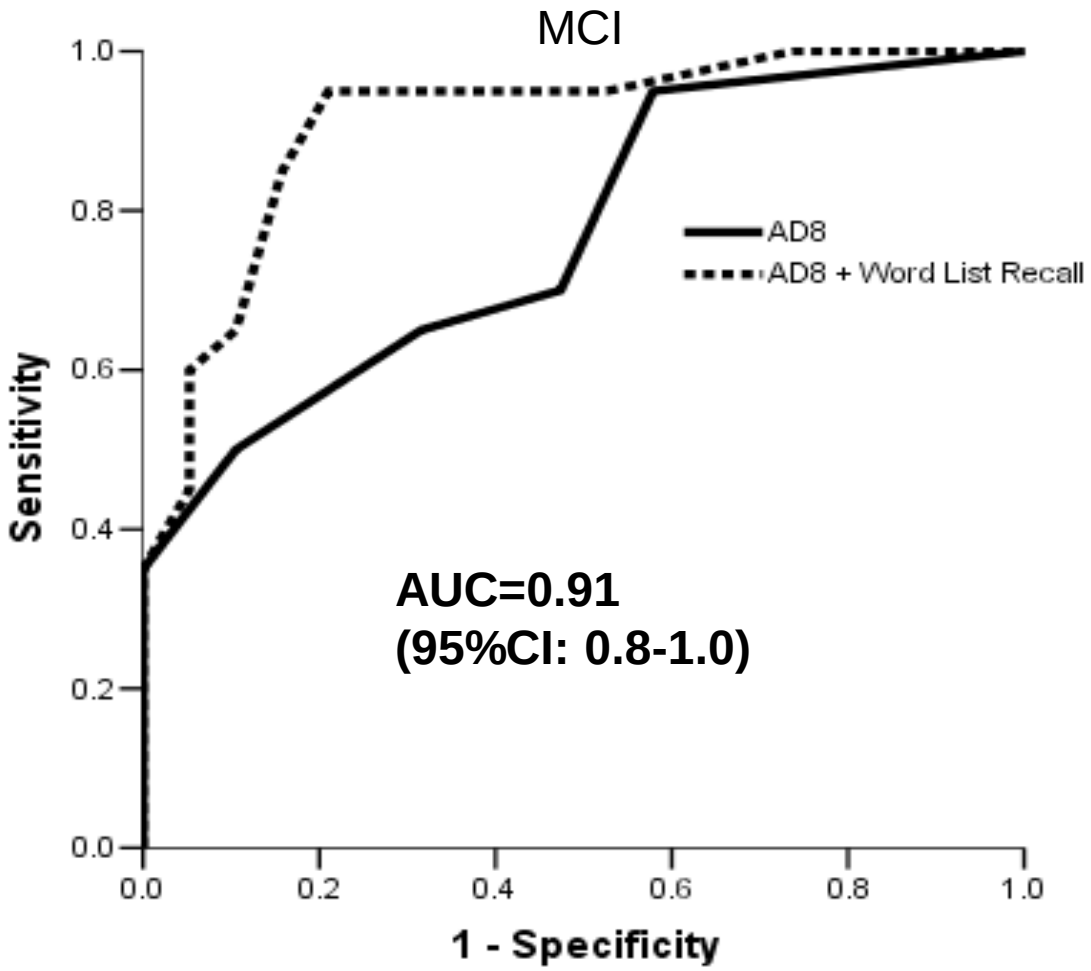


Diagnoses	AUC
No dementia	------
AD	0.958
VaD	0.984
Mixed AD/VaD	0.981
DLB	0.844
FTD	0.951
Aphasia ± memory	0.910
Mood disorder	0.929
Other cognitive disorders	0.874

Galvin JE et al, Neurology, 2006

Combining informant interview and performance





Combining a cut-off of ≥ 2 on the AD8 and ≤ 5 on 10-item word list recall:

Sensitivity: 94.1%	Sensitivity: 85.0%
Specificity: 81.8%	Specificity: 84.2%

Galvin JE et al, Archives Neurol 2007

QUICK DEMENTIA RATING SCALE

The following descriptions characterize changes in the patient's cognitive and functional abilities. You are asked to compare the patient now to how they used to be – the key feature is *change*. Choose *one answer* for

6. TOILETING AND PERSONAL HYGEINE	
0	Fully capable of self-care (dressing, grooming, washing, bathing, toileting)
0.5	Slight changes in abilities and attention to these activities

1. ATTENTION AND CONCENTRATION

□**0**	Normal attention, concentration and interaction with his/her environment and surroundings
□**0.5**	Mild problems with attention, concentration, and interaction with environment and surroundings, may appear drowsy during day
□**1**	Moderate problems with attention and concentration, may have staring spells or spend time with eyes closed, increased daytime sleepiness
□**2**	Significant portion of the day is spent sleeping, not paying attention to environment, when having a conversation may say things that are illogical or not consistent with topic
□**3**	Limited to no ability to pay attention to external environment or surroundings

0	Chores at home, hobbies and personal interests are well maintained compared to past performance
0.5	Slight impairment or less interest in these activities; trouble operating appliances (particularly new purchases)
1	Mild but definite impairment in home and hobby function; more difficult chores or tasks abandoned; more complicated hobbies and interests given up
2	Only simple chores preserved, very restricted interest in hobbies which are poorly maintained
3	No meaningful function in household chores or with prior hobbies

2	Significant portion of the day is spend sleeping, not paying attention to environment, when having a conversation may say things that are illogical or not consistent with topic
3	Limited to no ability to pay attention to external environment or surroundings
	COGNITIVE SUBTOTAL (QUESTIONS 1, 2, 3, 8)
	BEHAVIORALSUBTOTAL (QUESTIONS 4, 5, 6, 7, 9, 10)
	TOTAL QDRS SCORE

Properties of QDRS

Table 1: Properties of QDRS by Cognitive Status and Dementia Etiology

	Controls	MCI	AD	LBD	VaD	FTD	p-value
Age, y	70.1 (7.6)	76.2 (8.9)	79.8 (7.5)	78.4 (7.7)	77.2 (6.2)	72.7 (8.2)	.001
Education, y						16.8 (3.3)	.28
CDR						0.8 (0.8)	<.001
CDR-SB						5.2 (4.7)	<.001
MMSE						23.6 (1.4)	.005
Functional Activities Questio						8.1 (9.9)	.001
Neuropsychiatric Inventory	0.9 (1.6)	5.6 (4.7)	7.7 (5.7)	11.6 (5.7)	11.4 (5.6)	10.5 (9.1)	002
QDRS Total	0.3 (0.5)	3.5 (2.7)	7.2 (5.1)	11.7 (6.9)	11.6 (7.8)	7.4 (6.3)	<.001
QDRS Cognitive Subscale	0.2 (0.3)	1.5 (0.9)	3.1 (1.9)	4.5. (2.6)	2.8 (2.3)	2.7 (2.4)	.005
QDRS Behavioral Subscale	0.2 (0.3)	2.0 (2.0)	4.2 (3.5)	7.5 (4.9)	8.8 (5.9)	5.4 (4.8)	<.001

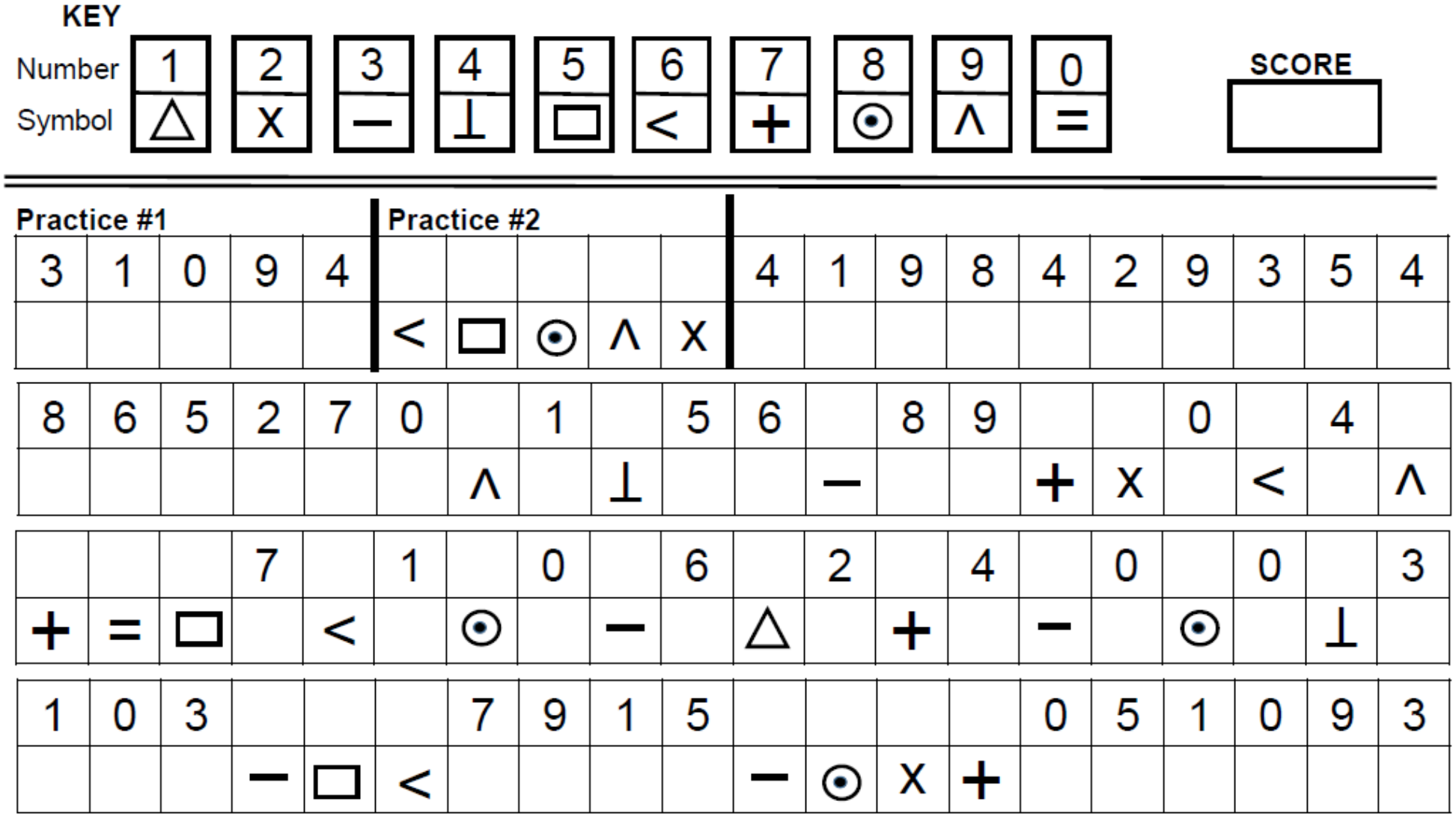
Key: AD=Alzheimer's Disease; LBD=Lewy Body Dementia; VaD=Vascular Dementia; FTD=Frontotemporal Degeneration; CDR=Clinical Dementia Rating; CDR-SB=CDR Sum of Boxes; MMSE=Mini Mental State Exam;

Normal	0-1
Mild cognitive impairment	2-5
Mild dementia	6-12
Moderate dementia	13-20
Severe dementia	20-30

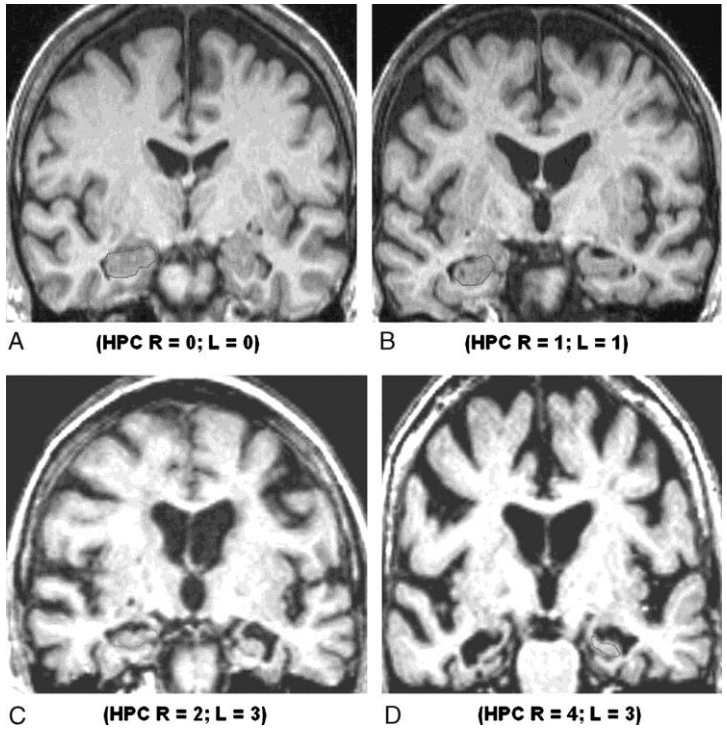
Lewy Body Composite Risk Score

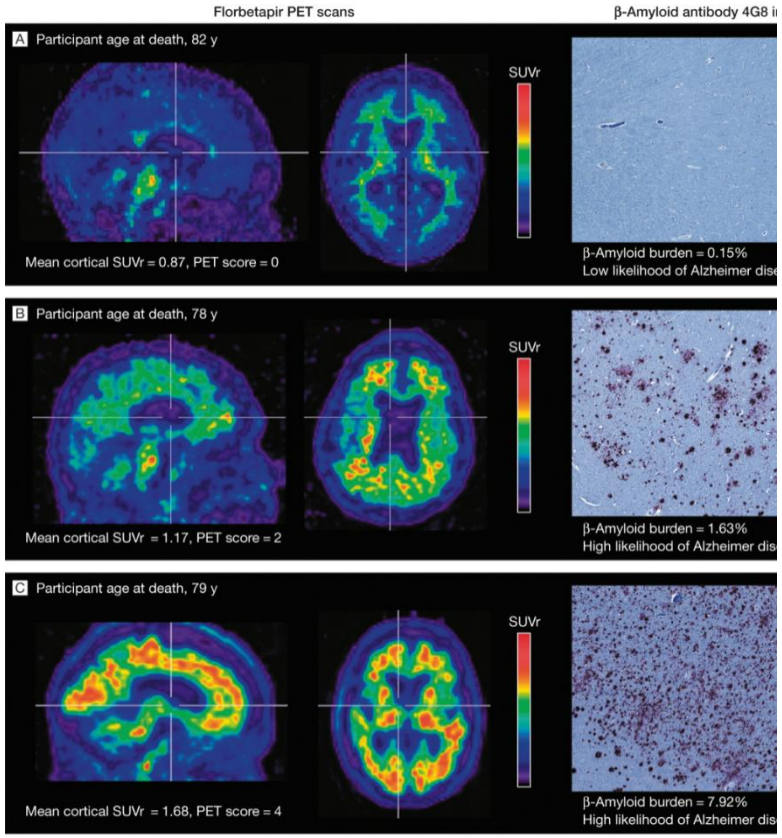
Please rate the following symptoms as being present or absent for at least 3 times over the past 6 months. Does the patient…	**Yes**	**No**
Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?		
Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?		
Have a loss of postural stability (balance) with or without frequent falls?		
Have a tremor at rest in any of the 4 extremities or head?		
Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?		
Have episodes of illogical thinking or incoherent, random thoughts?		
Have frequent staring spells or periods of blank looks?		
Have visual hallucinations (see things not really there)?		
Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?		
Have orthostatic hypotension or other signs of autonomic insufficiency?		
TOTAL SCORE		

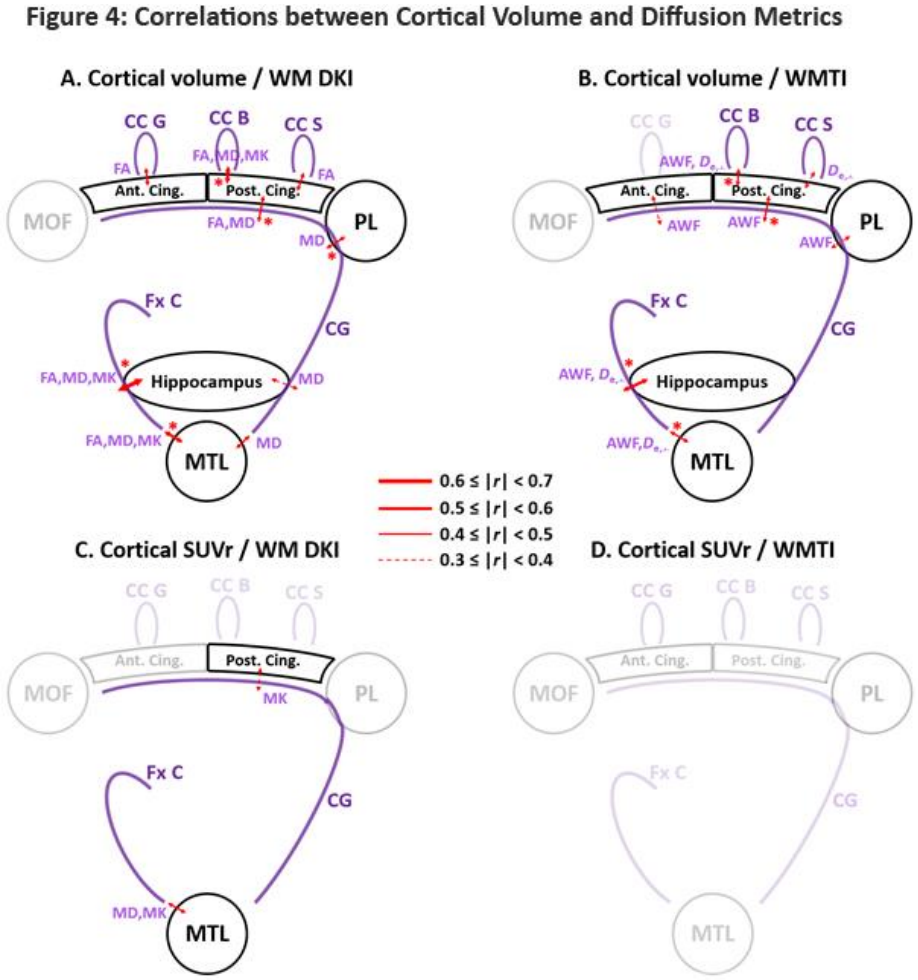
Number-Symbol Coding Test



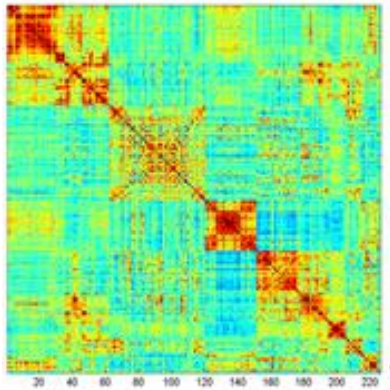
Relationship Between Imaging Biomarkers



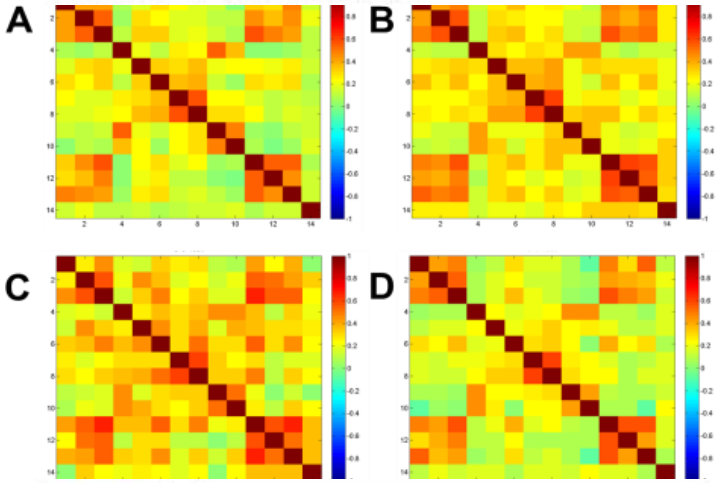


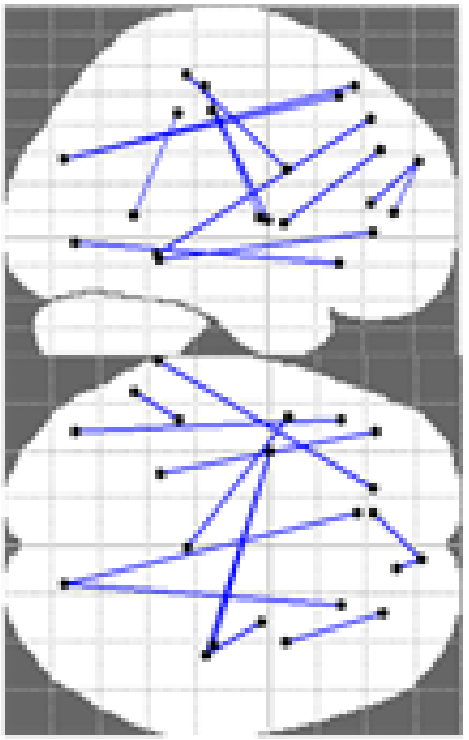


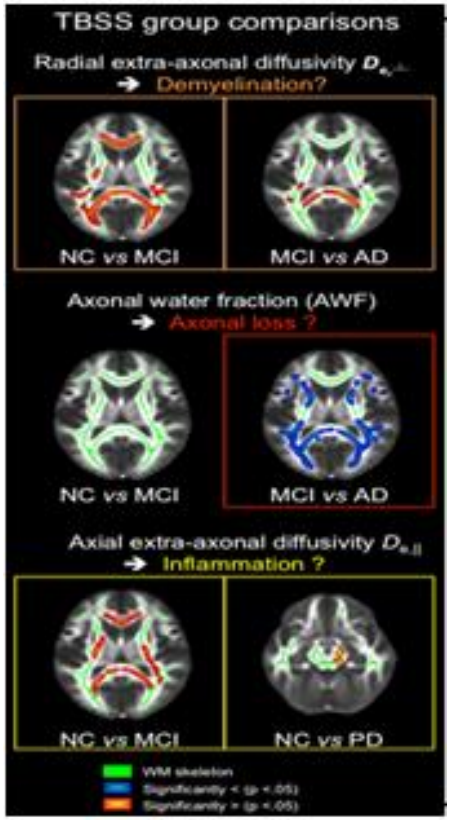
Structure-Function Connectome

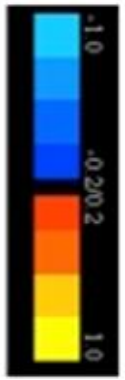


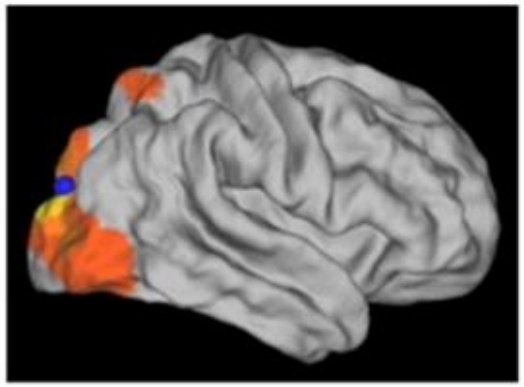
Sensory motor network
Cingulo-opercular network
Auditory network
Default mode network
Visual network
Fronto-parietal network
Salience network
Subcortical network
Attention network

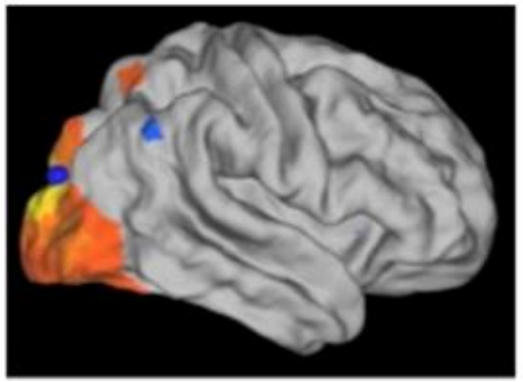


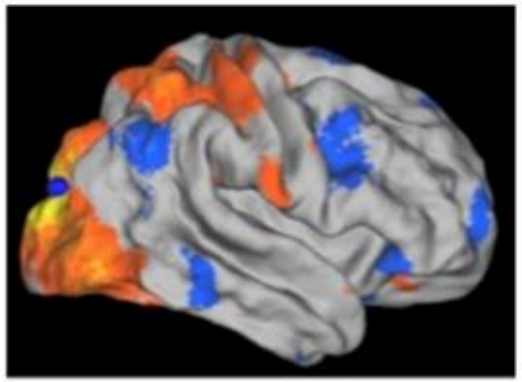




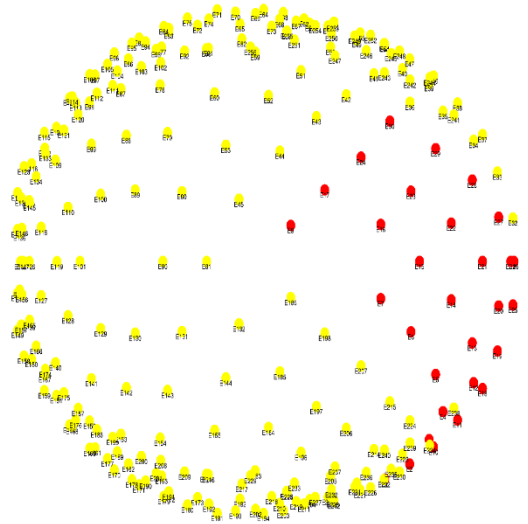


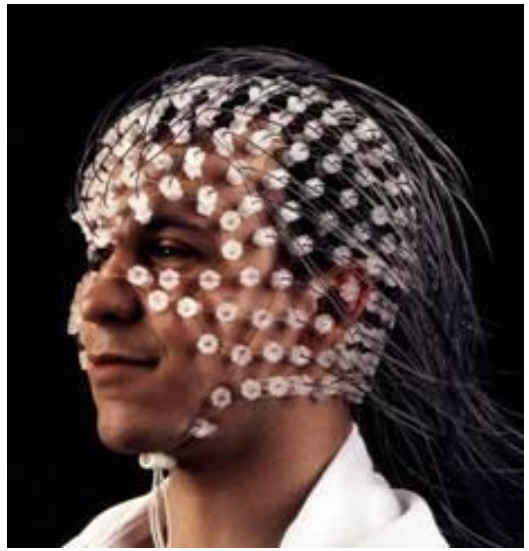


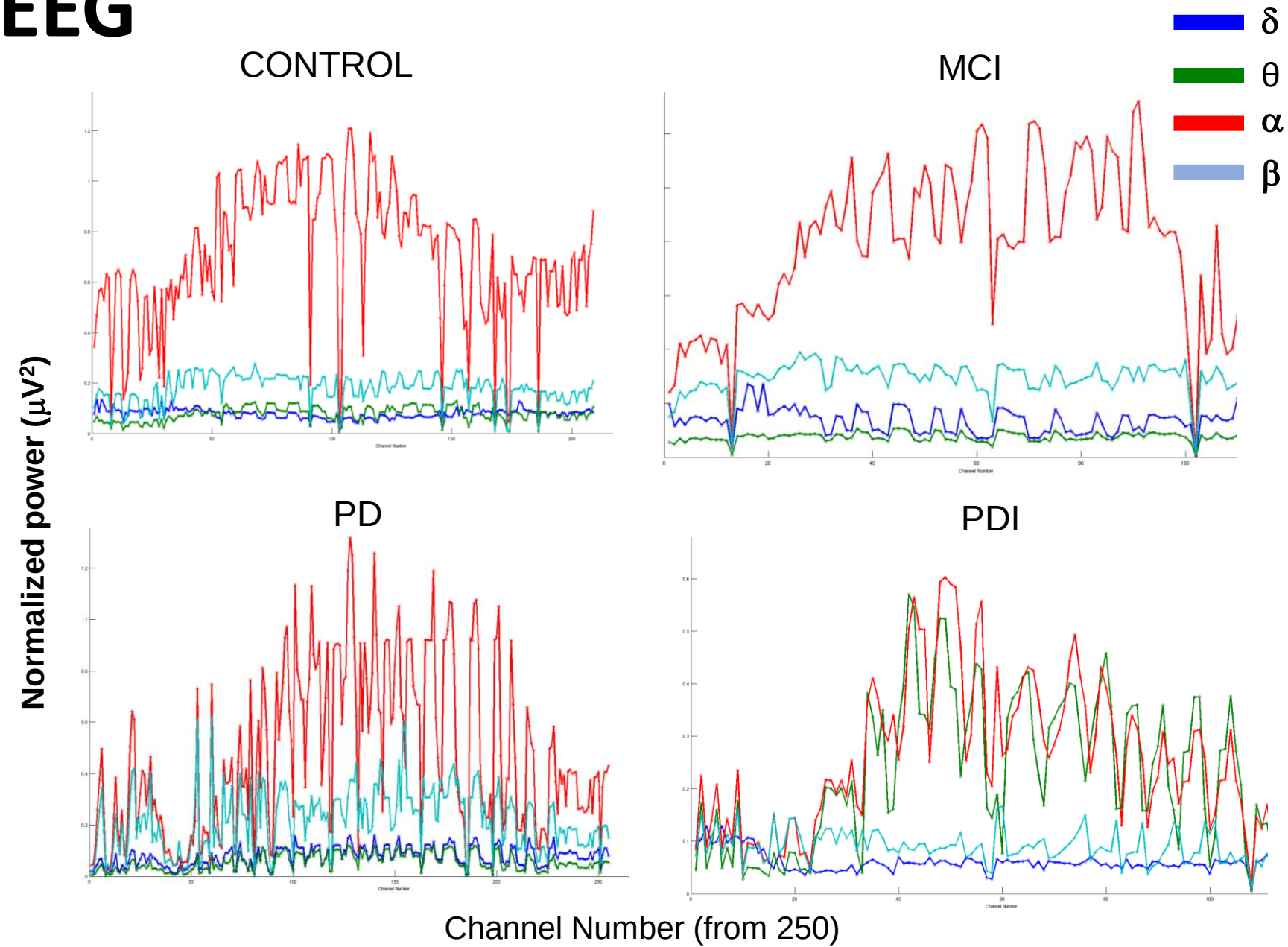




High Density EEG

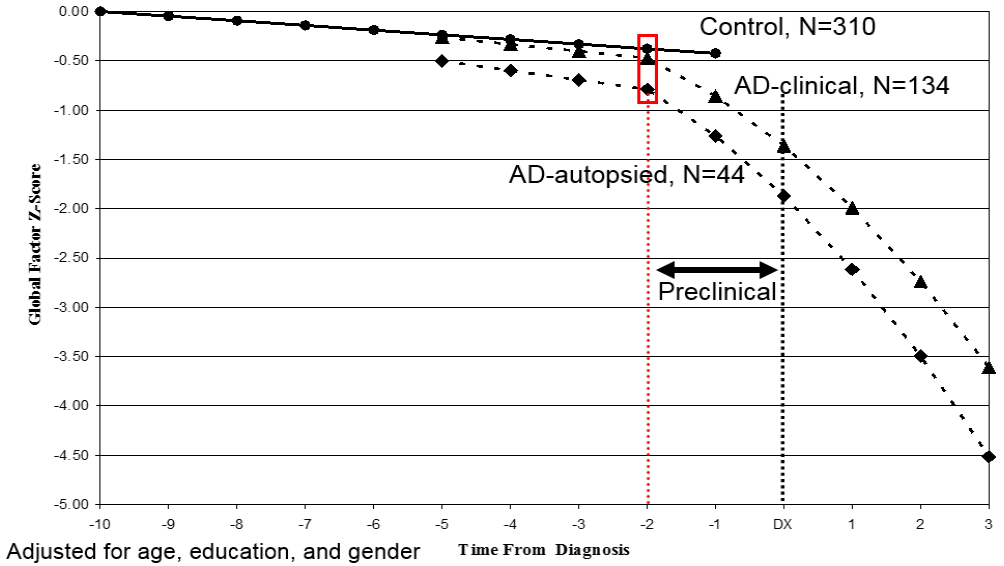




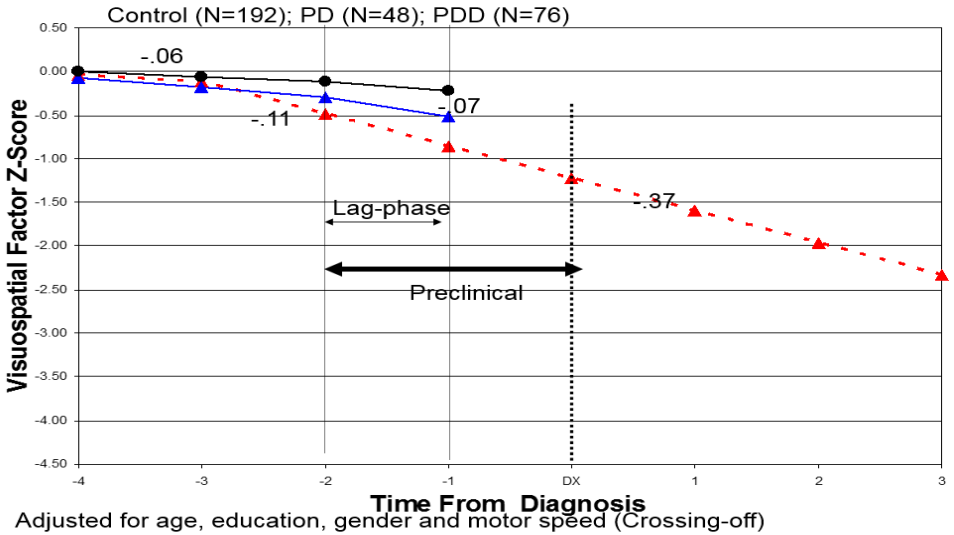


Modeling Neurodegenerative Diseases

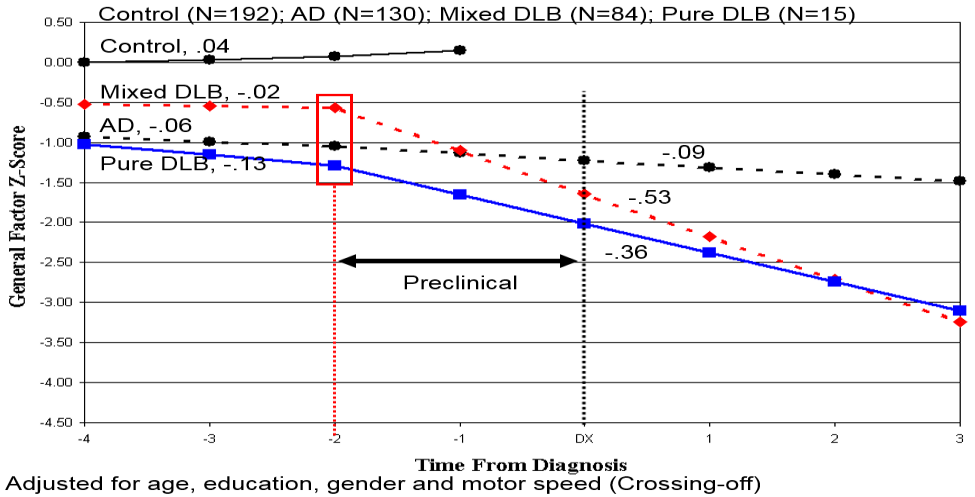
A: AD vs. Controls



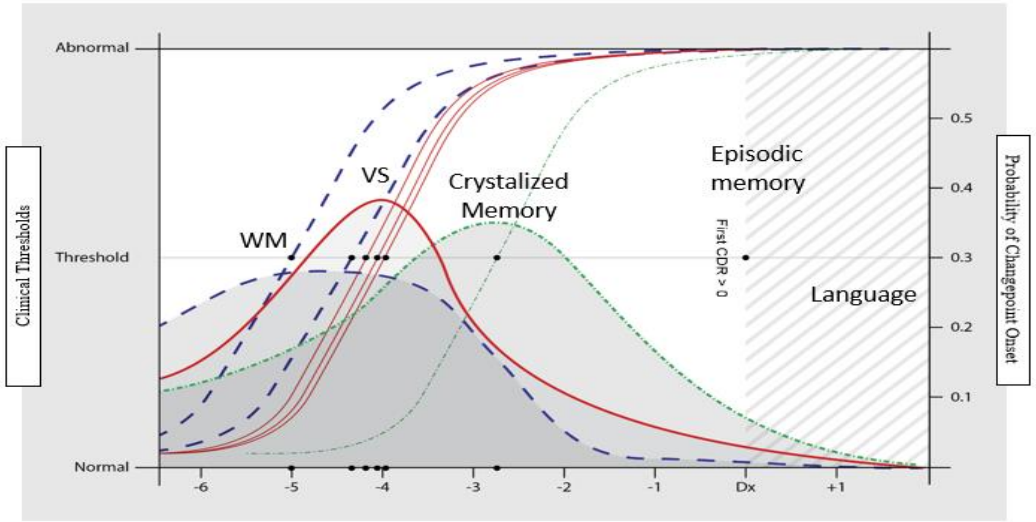
B: PD vs. PDD vs. Controls



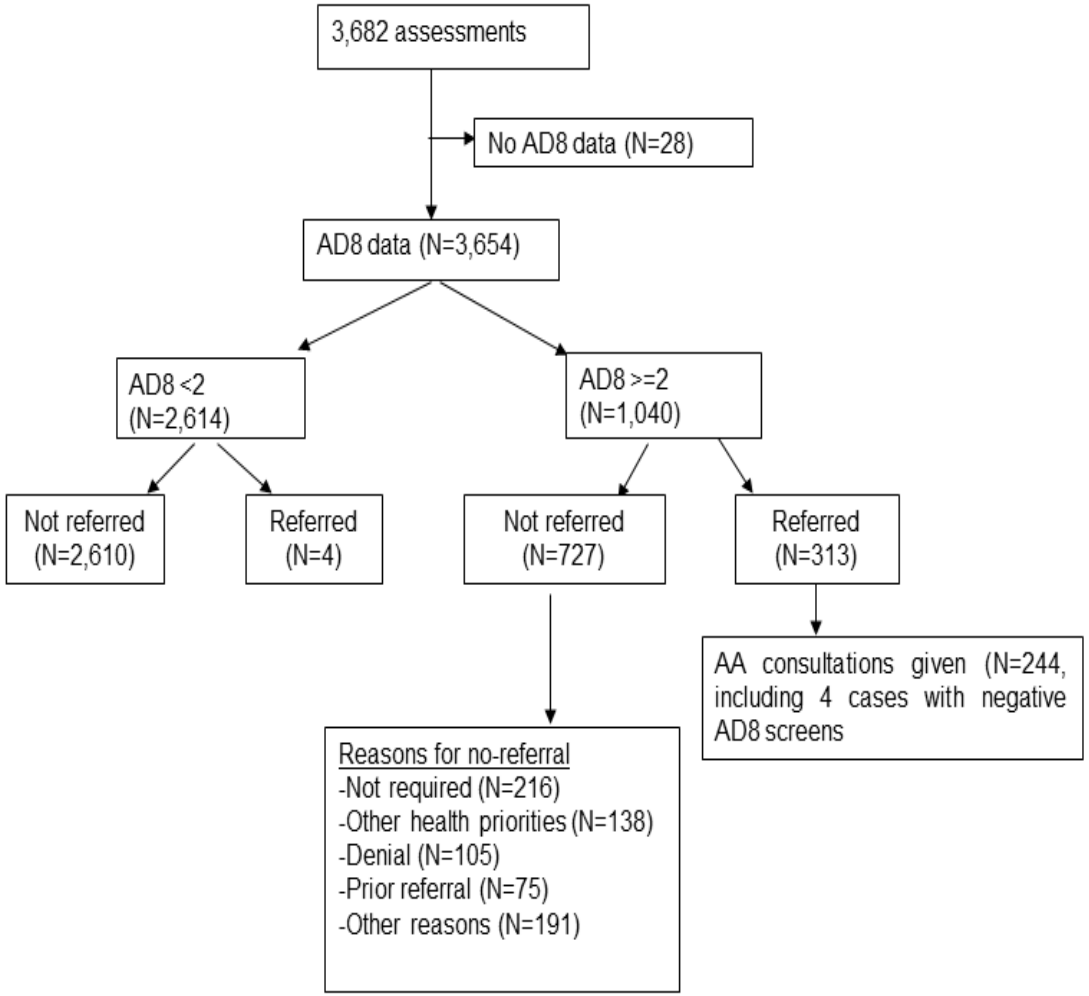
C: AD vs. DLB



D: Evolution of PD-MCI



Project LEARN MORE



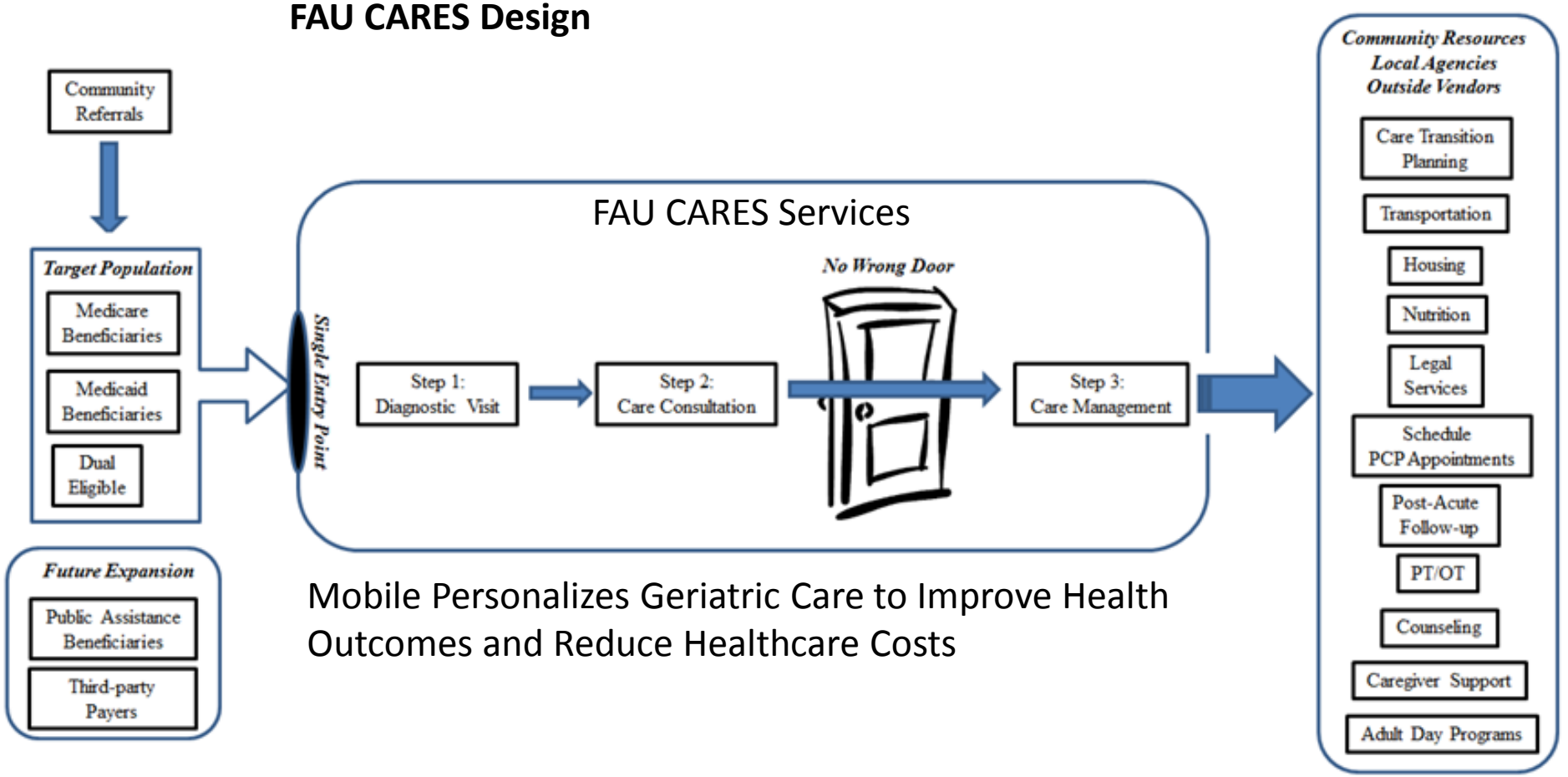
- Collaborative effort
  - Missouri Department of Health
  - 10 Area Agencies on Aging (AAA)
  - 4 Alzheimer Association chapters
  - Academic researchers
- 2 day training for AAA field workers
- Screened ~4000 older adults for dementia
- Incidence: 28.5%
- 244 referred for intervention
- Compared with 96 usual care controls
- Improved knowledge, mood, social support

Effect of Project Learn MORE on delay in transitions of care	
Odds Ratio[£]	3.32 (1.25,8.83[€])
Relative Risk Reduction (%)	64.10 (14.96,84.84)
Absolute Risk Reduction (%)	14.67 (3.70,25.64)
Number Needed to Treat	6.82 (3.90,27.03)

Galvin et al, *Clinical Interventions Aging* 2014

FAU Center for Advanced Redesign of Eldercare Services (*FAU CARES*)

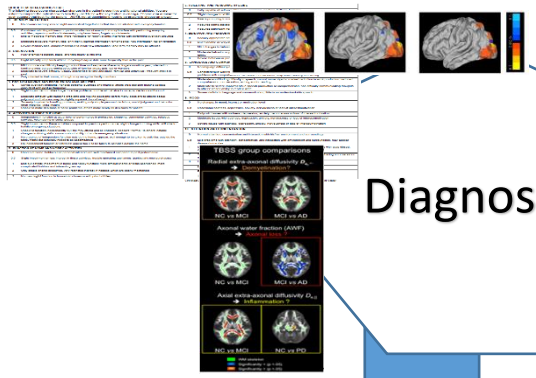
FAU CARES Design



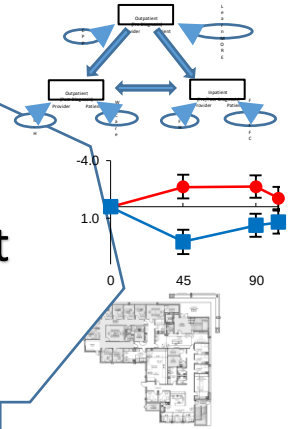
Mobile Personalizes Geriatric Care to Improve Health Outcomes and Reduce Healthcare Costs

Aging and Dementia Research Program

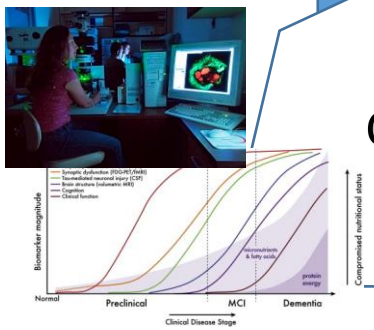
Diagnose



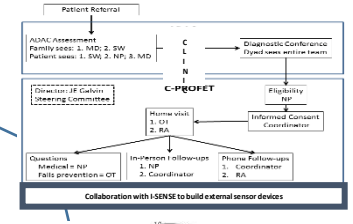
Treat

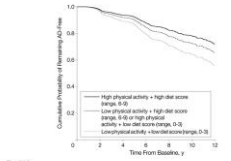


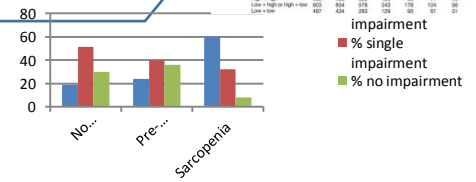
Cure



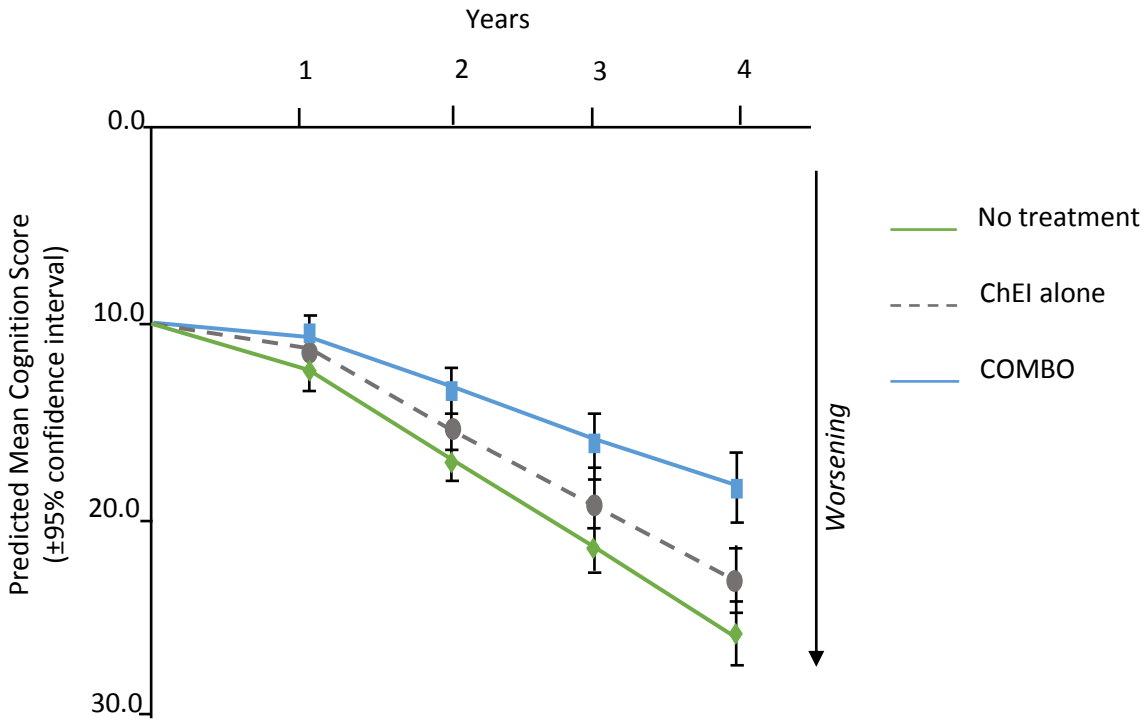
Prevent



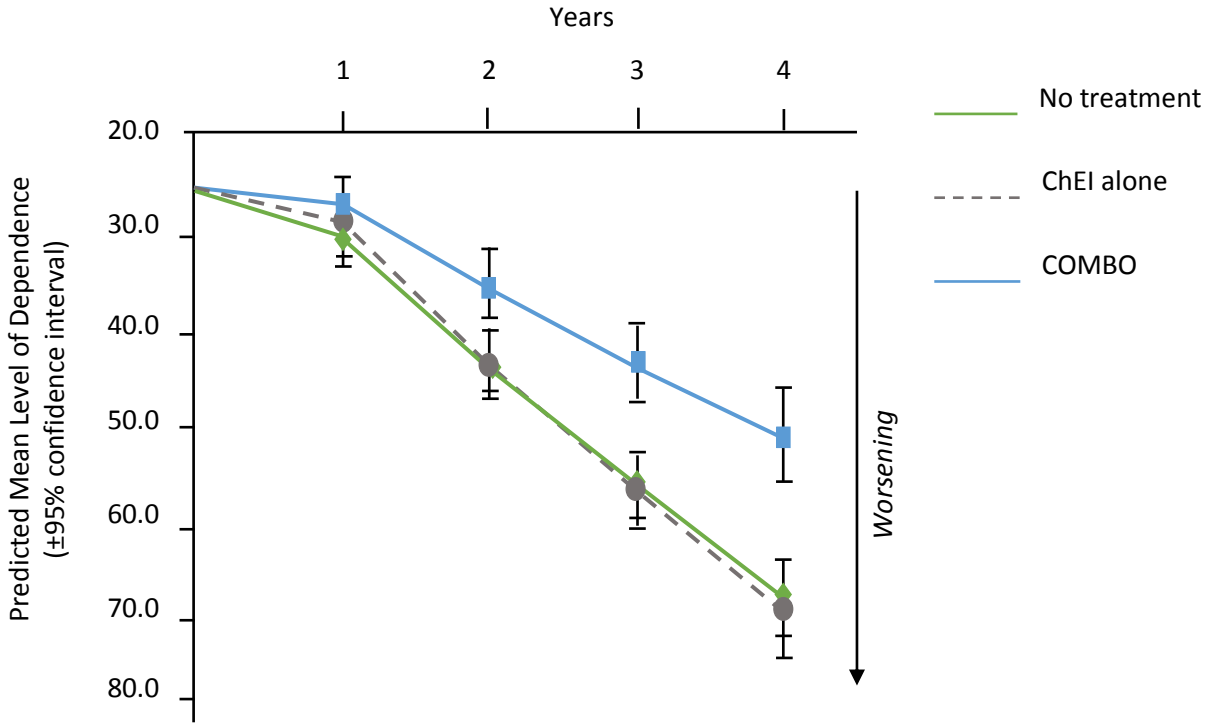




Combination Therapy: Long Term Effects

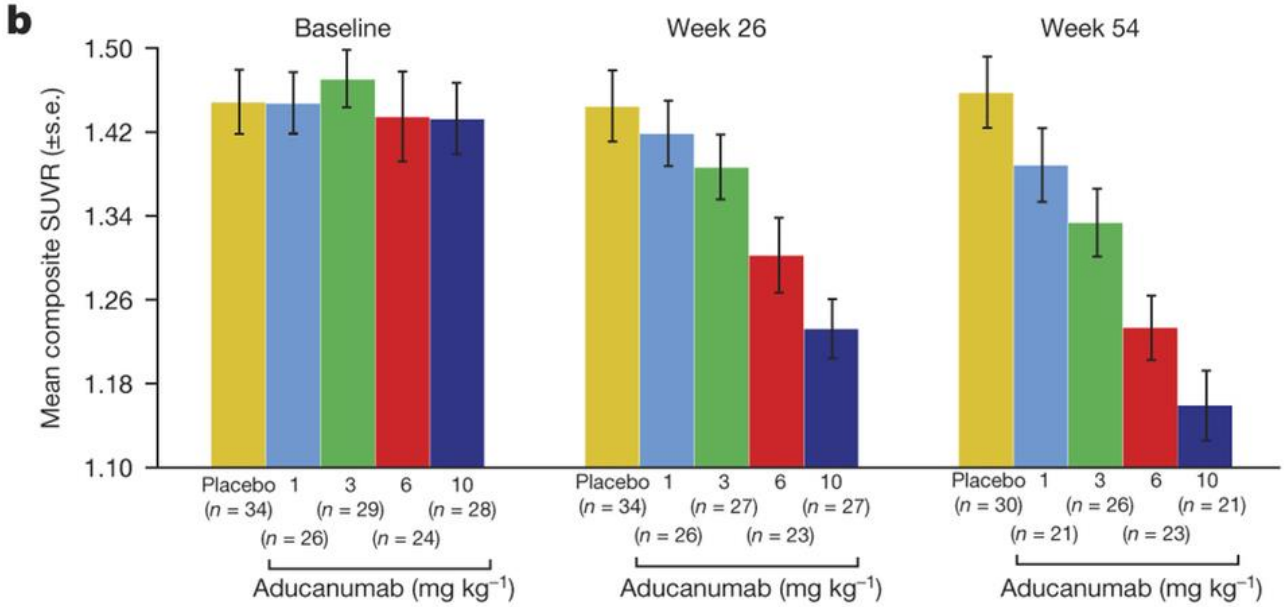


Cohen's d	1	2	3	4
ChEI alone vs no treatment	0.47***	0.39**	0.32**	0.23*
COMBO vs no treatment	0.56***	0.73***	0.76***	0.77***
COMBO vs ChEI alone	0.10	0.34**	0.44***	0.49***



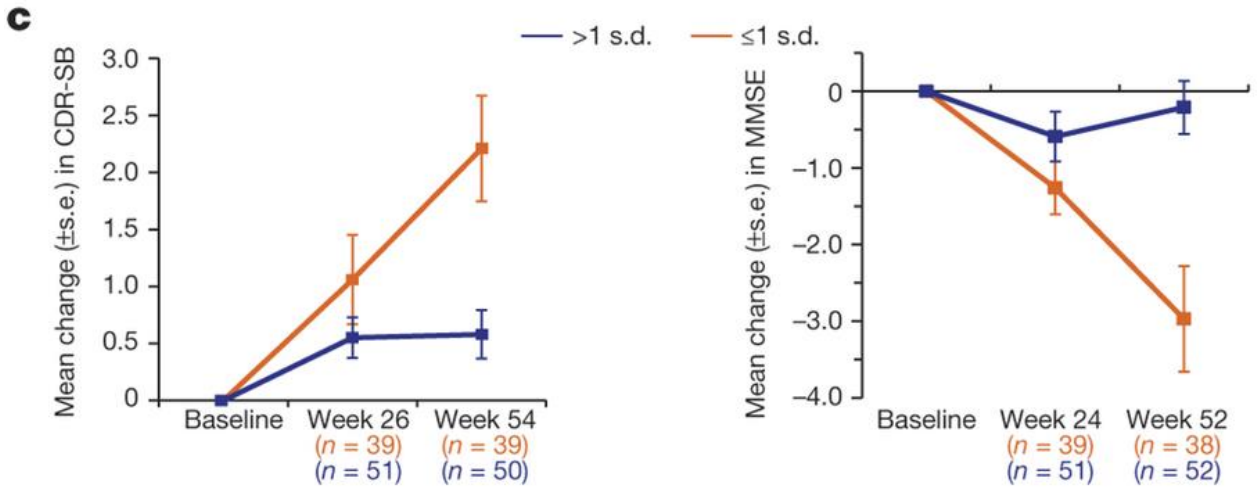
Cohen's d	1	2	3	4
ChEI alone vs no treatment	0.08	0.02	-0.03	-0.06
COMBO vs no treatment	0.32*	0.48***	0.60***	0.67***
COMBO vs ChEI alone	0.23	0.46***	0.62***	0.73***

Aducanumab Therapy for Alzheimer's Disease



Change in measurements of Amyloid B-protein over 54 weeks of trial demonstrating significant dose-response effect

Change in measurements of cognitive function (CDR-SB and MMSE) over 54 weeks of trial demonstrating significant treatment response



Sevigny J et al Nature 2016

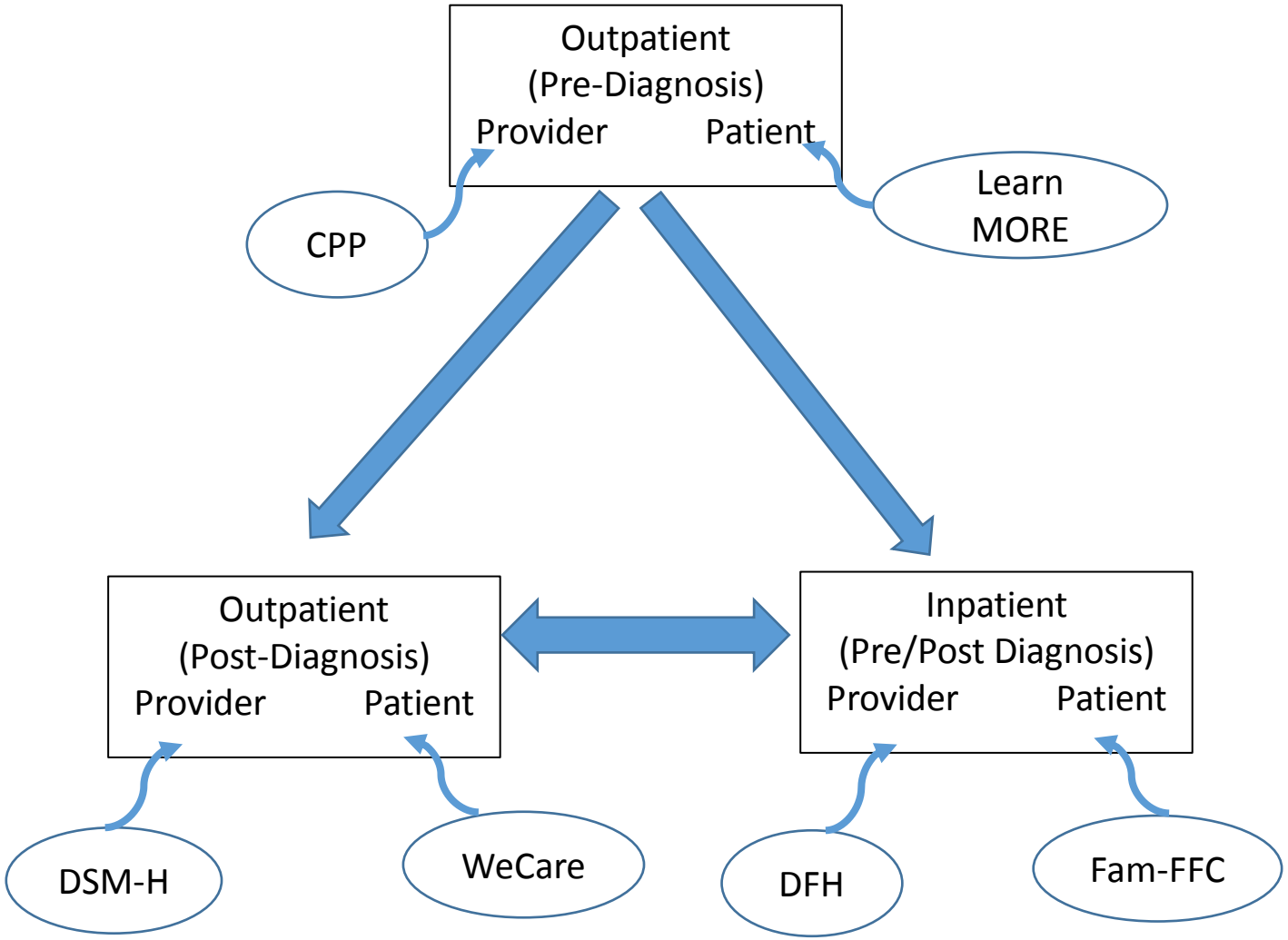
RVT-101 in Dementia with Lewy Bodies (DLB)

Significant unmet need: no drugs approved in the U.S. or EU	Cholinergic deficits are a prominent feature of DLB	Increasing acetylcholine improves cognition and function in DLB	$5HT_{2A}$ activity is a driver of visual hallucinations
Aricept was approved in Japan for the treatment of DLB in 2014	*Cholinergic neurotransmission is more dysfunctional in DLB than Alzheimer's disease*	*RVT-101 promotes the release of acetylcholine*	*RVT-101 inhibits the activity of the $5HT_{2A}$ receptor*

- ***24-week Phase 2b study***

Single successful study could serve as basis for approval of RVT-101 in DLB when combined with Alzheimer's filing

Interprofessional Education Initiatives



Clinician Partners Program: 3-day internship for rural clinicians. Increased care and diagnostic confidence and to significant practice change

Dementia Friendly Hospital Program: Training program for hospital staff. Increased knowledge and care confidence, increased dementia recognition of dementia, and creation of new programs to improve hospital discharge outcomes.

Project Learn MORE: State-wide intervention to increase dementia detection. Significant increases in dementia detection with appropriate referrals for resources, delays in nursing home placement and reduced mortality.

Family-centered, Function Focused Care: Program to incorporate family caregivers into hospital discharge planning teams. Increased caregiver preparedness, reduced caregiver anxiety, increased patient mobility, reduced post-discharge delirium, and reduced 30-day readmission rates.

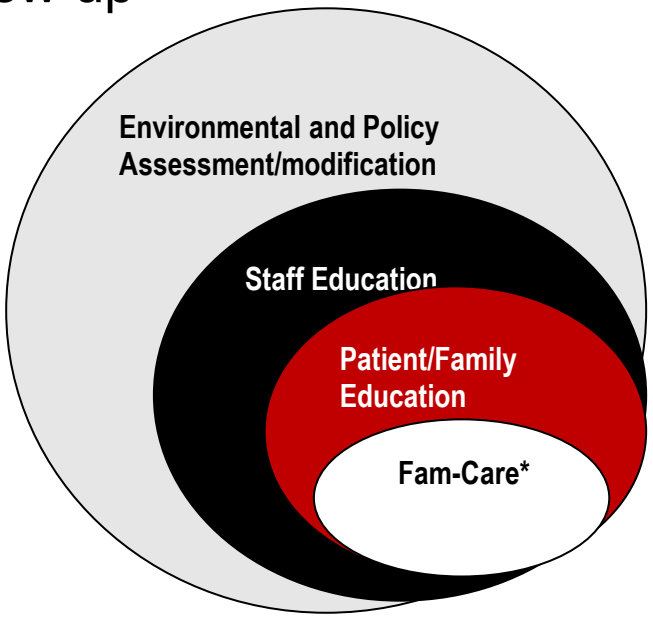
WeCare: Demonstration of a transdisciplinary collaborative care model. Increased caregiver and patient confidence, reduced caregiver burden, and increased patient satisfaction with care.

Dementia Symptom Management at Home: Program to improve home health care. Increased provider knowledge and confidence.

Family-centered, function-focused care (Fam-FFC)

A multi-component, educational- empowerment intervention to improve functional outcomes and patient/family experience

- Draws upon function-focused care work in long-term care and the community
- Adapted to acute care with improved functional outcomes
- Jointly-developed treatment goals, care plans, discharge planning, post-acute follow-up



Patient Outcomes 2 months post-discharge:

- Reduced Delirium (p=.03)
- Improved ADL (p=.02)
- Improved Walking Performance (p=.001)

Family Caregiver Outcomes 2 months post-discharge:

- Increased Preparedness (p=.04)
- Reduced Anxiety (p=.008)

Hospital Outcomes	Non-Intervention	Intervention	p-value
Discharge to nursing home	11 (26)	12 (27)	.56
Utilization of post-acute rehabilitation	27 (64)	29 (66)	.69
Readmission to hospital within 30 days	10 (24)	3 (7)	**.02**
Delirium 2 months post-discharge	12 (29)	3 (7)	**.05**
Failed to return to baseline function 2 months post-discharge	21 (15)	5 (12)	**.003**
Length of stay	4.4 (2.0)	4.0 (2.1)	

Resnick et al., 2006, 2009, 2011, Boltz et al, JAGS, Boltz M et al Neurodegen Dis Manag, 2015

Quality Improvements in Dementia Care

- Determination of presence and severity of differential diagnosis of the specific type of dementia
- Evaluation for reversible causes of dementia
- Appropriate use of medical tests and evaluations
- Active case finding and treatment for excess disability due to comorbid medical conditions and assessment of impact of co-morbid diseases on cognitive status
- Active case finding and treatment for patient depression, psychoses, behavioral disturbances, sleep disorders, and hazardous activities (e.g., driving, alcohol and substance abuse)
- Active case finding for caregiver burden and depression and ascertainment of family dynamics
- Needs assessment of patient-caregiver dyad
- Pharmacotherapy of dementia syndrome with stage-appropriate medications
- Referral for physical, occupational, speech and language, cognitive therapies
- Non-pharmacological therapies for psychological and behavioral disturbances
- Consideration and close monitoring of pharmacotherapy for behavioral disturbances
- Referral to patient and caregiver educational programs and/or community support agencies
- Counseling and care coordination services
- Facilitated communication between all clinicians involved in patient care
- Active surveillance and tracking of patient- and caregiver-centered outcomes
- Active monitoring and support of the caregiver's emotional and physical health
- Development of transition-in-care plans and appropriate referrals for palliative and hospice services

Galvin JE, Valois L, Zweig Y. Collaborative transdisciplinary team approach for dementia care. Neurodegener Dis Manag 2014;4:455-469.

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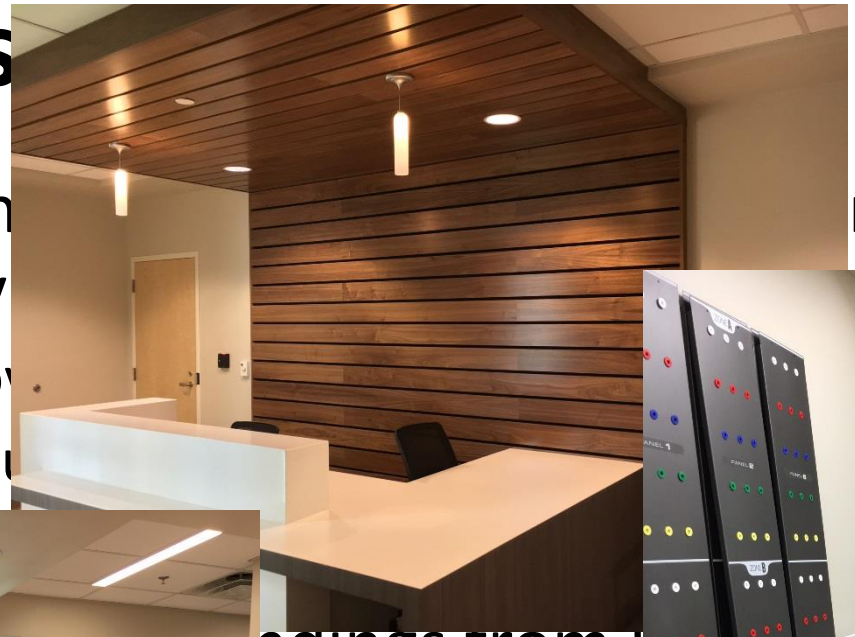
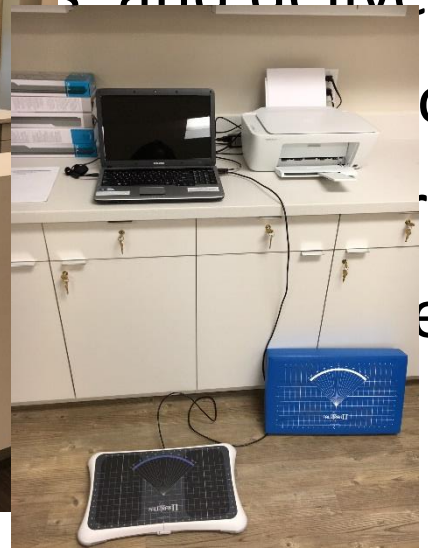
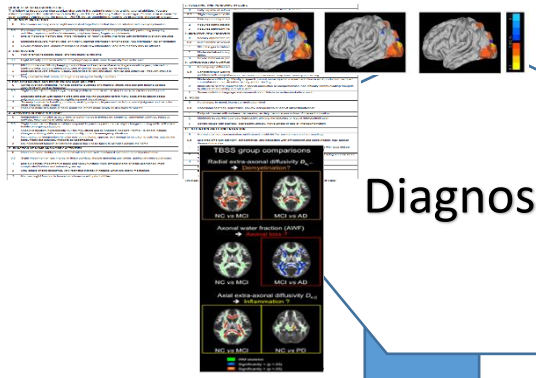


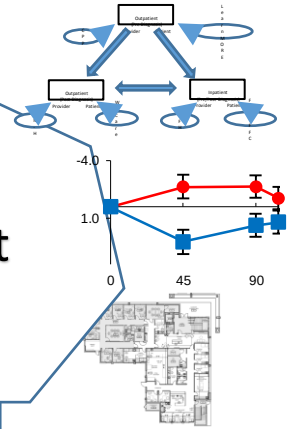


Aging and Dementia Research Program

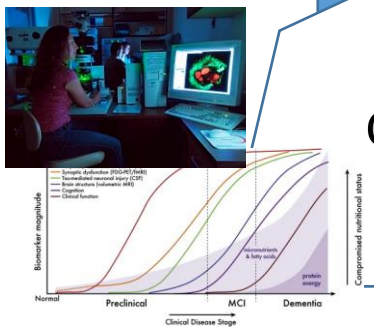
Diagnose



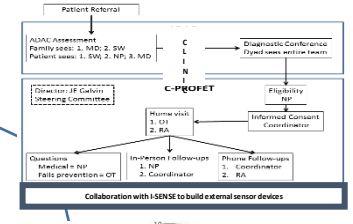
Treat

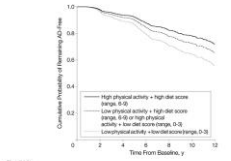


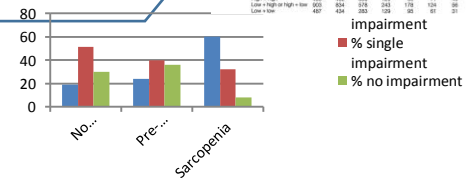
Cure



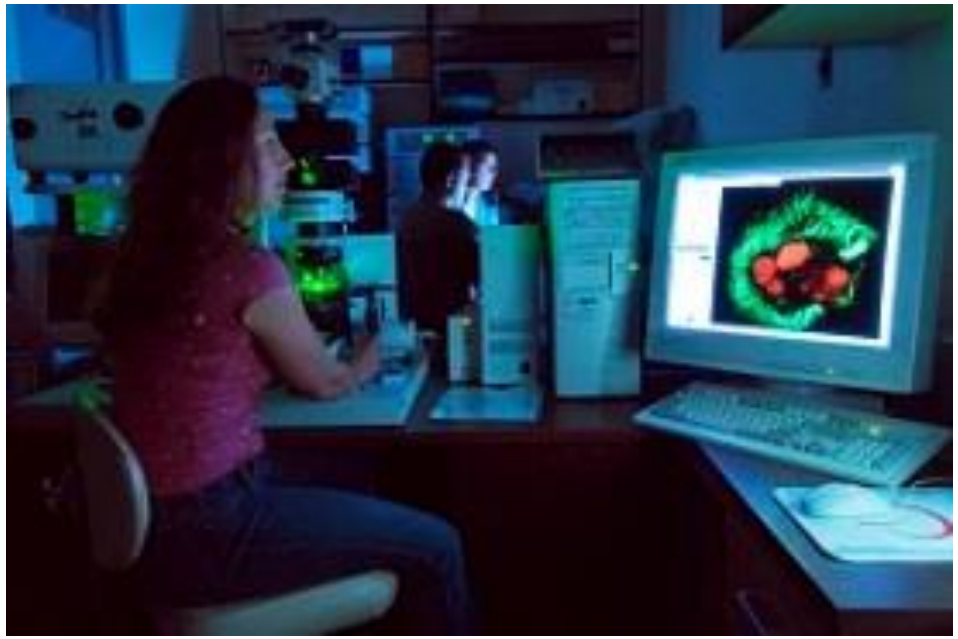
Prevent







Marine Biomedical & Biotechnology Research



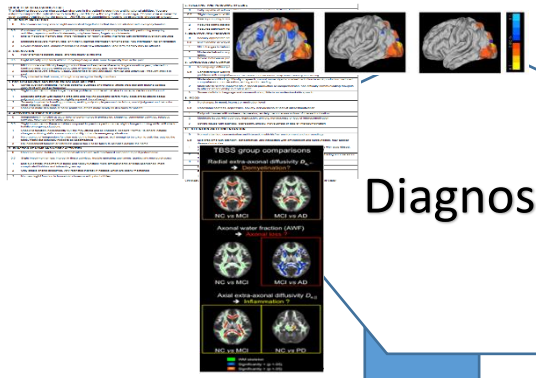
- Oceans cover over 70% of the earth's surface and within them there is an amazing diversity of life
- Developing therapeutic products from natural sources
- Support multi-disciplinary research projects exploring ocean-based drug discovery
- Sample library from deep fore reefs, vertical walls, and boulder zones covering Atlantic and Caribbean waters with additional samples from Galapagos, Western Pacific, Mediterranean, Indian, West African, and Bering Seas

Dementia Treatment and Cure Initiative

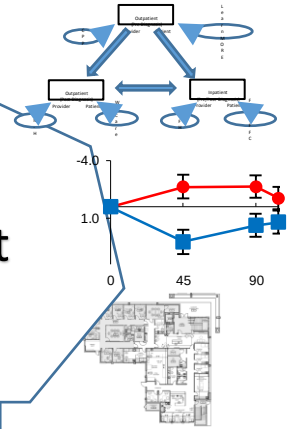
- Specialty unit dedicated to developing, testing, and validating new treatments to prevent, treat, or cure dementia
- Tie in with basic science and drug discovery efforts at Harbor Branch and Jupiter campuses, Scripps, and Max Planck
- Dynamic network of clinical, translational, and basic scientists working on developing novel molecules
- Move promising ideas from the lab to the patient (“bench” to “bedside”) considerably faster than a traditional research environment

Aging and Dementia Research Program

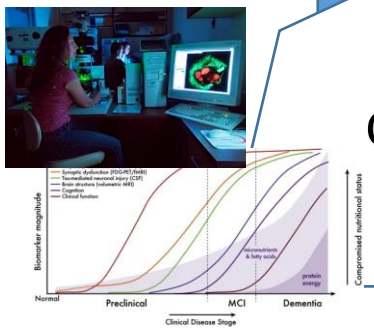
Diagnose



Treat



Cure



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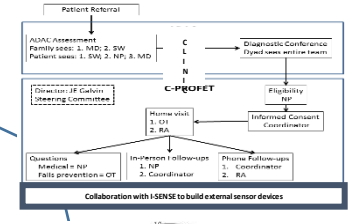
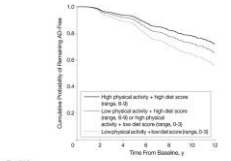
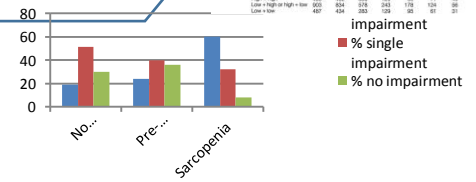
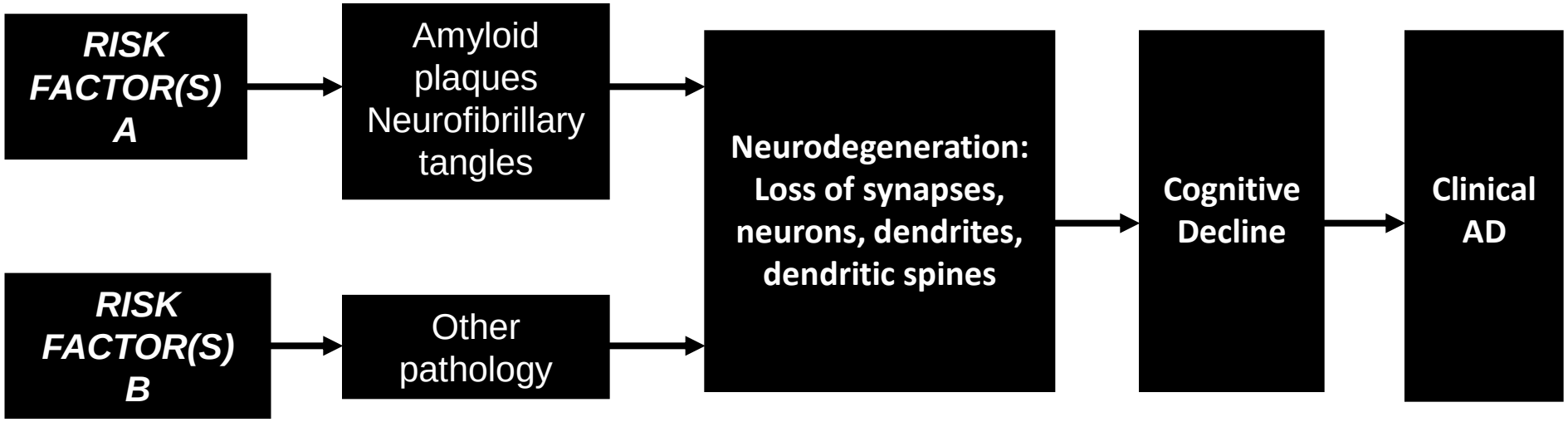






Clinical Expression of AD may evolve from different etiologies



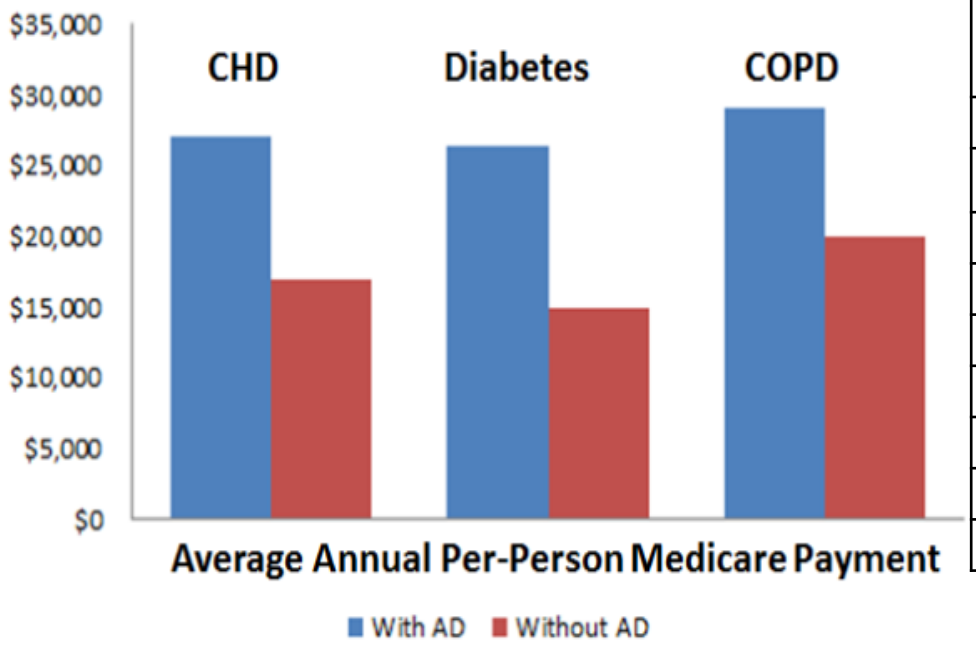
- Can prevent or treat AD by addressing:
  - AD pathology (plaques, tangles)
  - Other pathologies and mechanisms

Adapted from Bennett DA, et al. *Neurology*. 2009;72:1495-1503.

Multiple Chronic Conditions (MCCs) and AD

- Coronary heart disease (CHD), diabetes mellitus (DM), and Alzheimer's disease and related dementias (AD) affect older adults of all backgrounds, but may be more prevalent in minority populations
- MCCs often have complex, bidirectional relationships with each other
- Poorly recognized and controlled medical conditions may increase the risk of cognitive impairment
  - CHD and DM increase the risk of AD
  - AD leads to poor compliance, worse health outcomes, and increased costs in CHD and DM

Figure 1: Average Costs for Chronic Conditions with or without Alzheimer's Disease



Source: Alzheimer Association Facts and Figures 2012

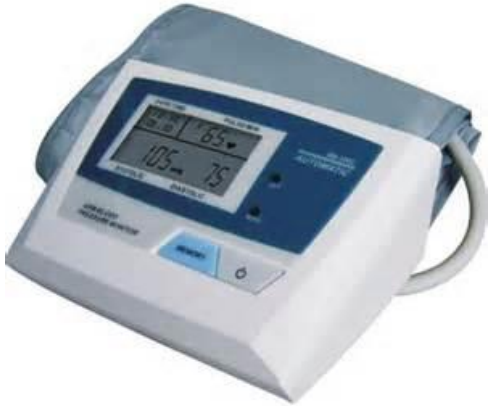
Prevalence of Chronic Disease in Medicare Beneficiaries (2013 Data)				
	National	Florida	Palm Beach County	Broward County
Beneficiaries	34,126,305	2,243,566	174,150	119,379
Alzheimer's Disease[1] (%)	**9.8**	**11.3**	**11.5**	**12.7**
Depression (%)	15.4	16.4	15.2	17.9
Coronary Heart Disease (%)	28.5	37.1	42.7	37.8
Diabetes (%)	27.0	28.5	28.9	29.1
COPD (%)	11.9	13.6	9.7	12.4
Hypertension (%)	55.5	60.8	60.3	58.8
Hypercholesterolemia (%)	44.7	55.5	60.2	52.9
Strokes (%)	3.8	4.5	4.6	4.8

Multicultural Community Dementia Screening

- Supported by 2 grants from the National Institute on Aging
- Community-based assessment of older adults (target goal 500)
  - Demographics, financial resources, preferences
  - Cognitive-Behavioral Screening (memory, mood)
  - Medical Screening (blood pressure, diabetes, lung disease, obesity)
  - Physical assessment (balance, frailty, strength)
  - Anthropometric measurements
  - Social work follow-up
- Subset have Gold Standard testing and biomarkers collected
  - MRI scans
  - PET scans
  - EEG
  - Blood and Spinal fluid
- Repository of multicultural medical, cognitive, and imaging biomarker data: 500 individuals with grant protocol (187,500 data points); a subset of 150 individuals with a Gold Standard evaluation (202,500 data points), structural and functional MRI, FDG-PET (SUVR), and high density EEG (125,000 data points) + raw and processed images.

Measurement Tools

Body Composition
Impedance

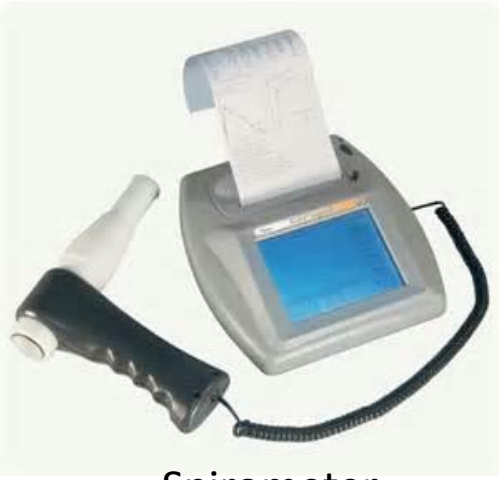


Sphygmomanometer
Blood pressure

Dynamometer
Grip Strength

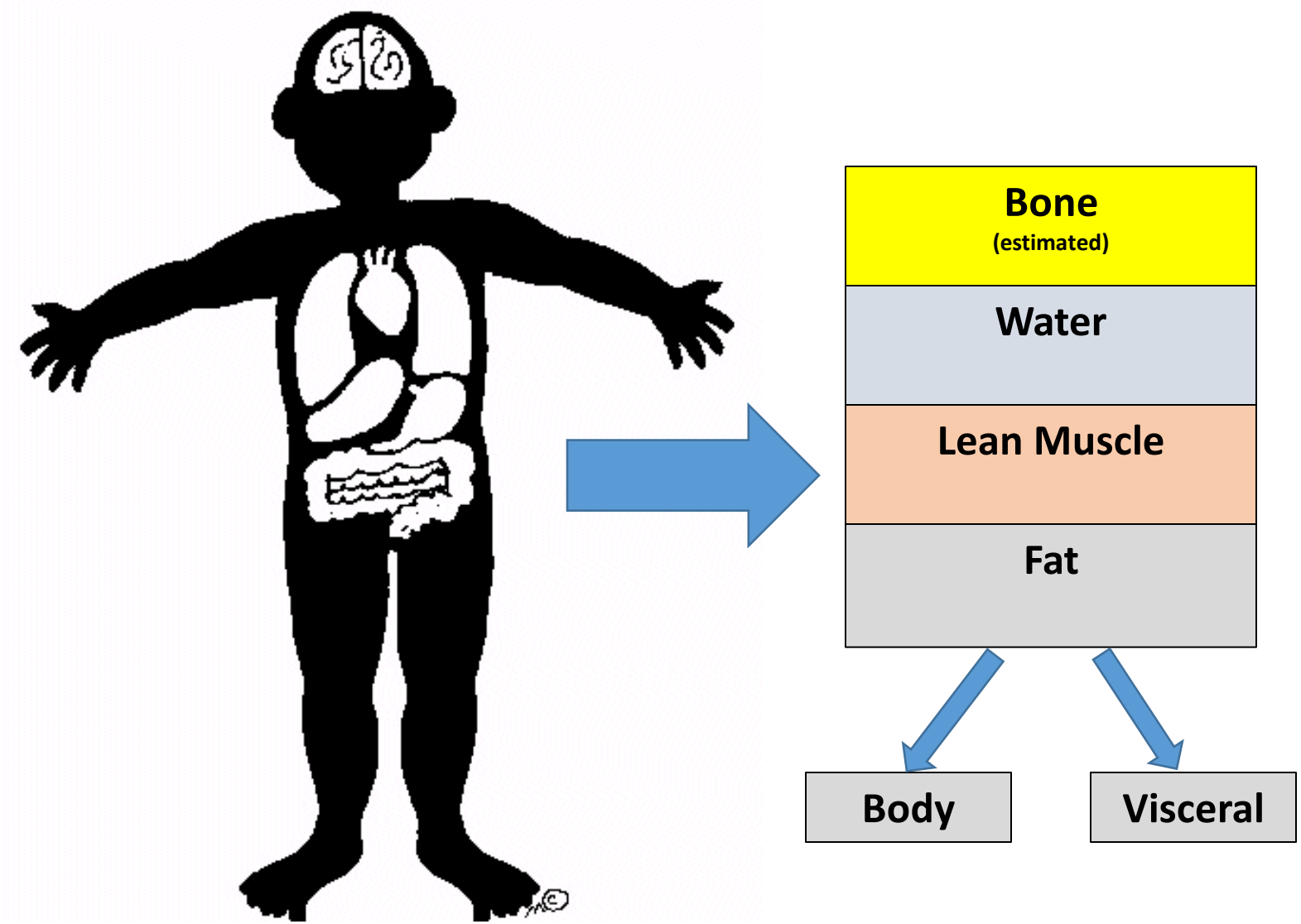
Hemoglobin A1C meter
Diabetes Risk

Stopwatch/Tape Measure



Spirometer
Forced Expiratory Volume

Body Composition



Diabetes and the Risk of AD

Diabetes mellitus	Total population*	Men†	Women†
All	1.9 (1.3 to 2.8)	1.8 (0.8 to 4.1)	1.9 (1.2 to 3.0)
No drug treatment	1.3 (0.7 to 2.3)	1.4 (0.5 to 4.0)	1.3 (0.7 to 2.6)
Oral medication	2.4 (1.4 to 4.1)	2.2 (0.7 to 7.4)	2.4 (1.3 to 4.4)
Insulin treatment	4.3 (1.7 to 10.5)	3.9 (0.5 to 29.5)	4.3 (1.6 to 11.8)

Subjects without diabetes served as reference. Values are relative risk (95% CI).

* Adjusted for age and sex.
† Adjusted for age.

Dementia subtype	Relative risk (95% CI)
Total AD	1.9 (1.2 to 3.1)
Without cerebrovascular disease	1.8 (1.1 to 3.0)
With cerebrovascular disease	3.0 (1.0 to 9.3)
Vascular dementia	2.0 (0.7 to 5.6)
Other dementias	1.6 (0.5 to 5.0)

Subjects without diabetes served as reference.

Ott A, et al Neurology 1999

Elevated Hemoglobin A1C and Cognitive Impairment

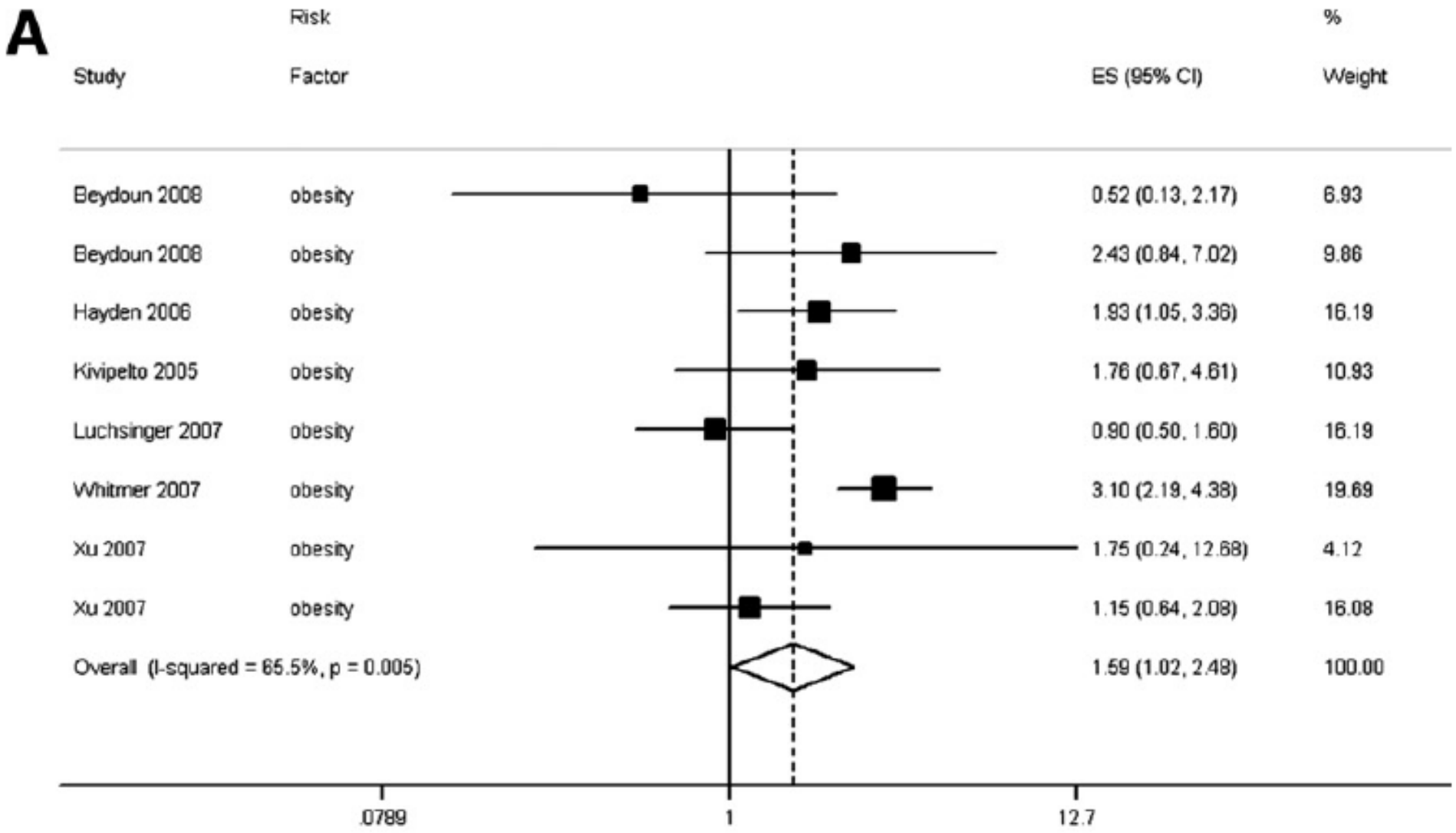
- Hemoglobin A1C relates to average plasma glucose concentration over previous 2-3 months
- Higher amounts of A1C indicates diabetes risk, poorer control of blood glucose, and risk of heart, kidney and retinal disease
  - For diabetics, goal is below 6%
- Categories
  - Normal (reference): ≤ 5.6%
  - Pre-diabetes: 5.7-6.4%
  - Diabetes: ≥ 6.5%

Adjusted Regression Model

	B	Std Error	Sig	Exp(B)	95% CI
Age	.019	.030	.519	1.02	0.96 – 1.08
Gender	-.421	.606	.49	.657	0.20 – 2.15
Pre-diabetes	.129	.675	.85	1.14	0.30 – 4.27
Diabetes	1.58	.785	.04	4.88	1.05 – 22.72

Diabetes increases risk of cognitive impairment 4.8-fold

Obesity and risk of AD



Profenno et al, Biol Psych 2010

BMI Increases Risk of Cognitive Impairment

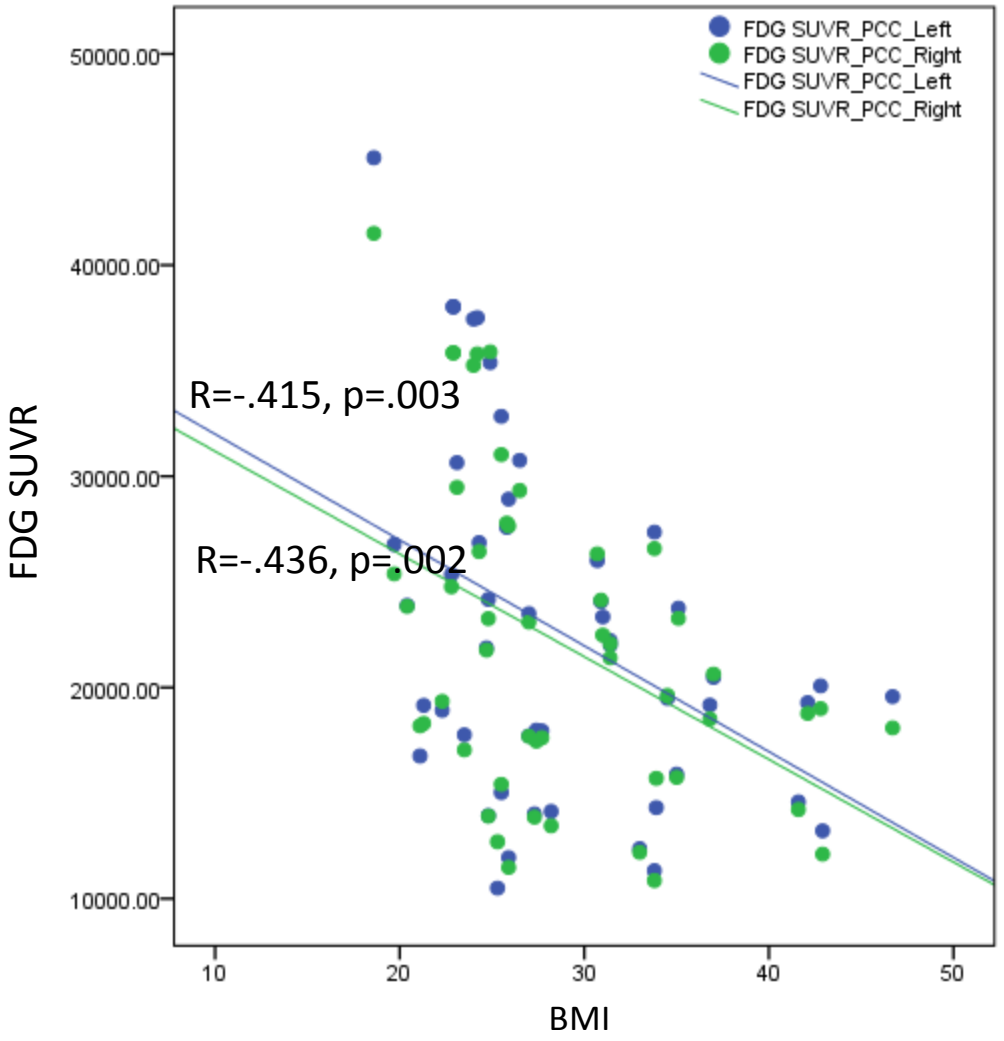
Adjusted Regression Model for BMI

	Exp(B)	95% CI
Age	1.04	1.01 – 1.07
Gender	.577	.33 – 1.01
BMI 25-29.9	1.51	0.82 – 2.76
BMI ≥ 30	2.20	1.13 – 4.32

Lean BMI = (1-%body fat * BMI)

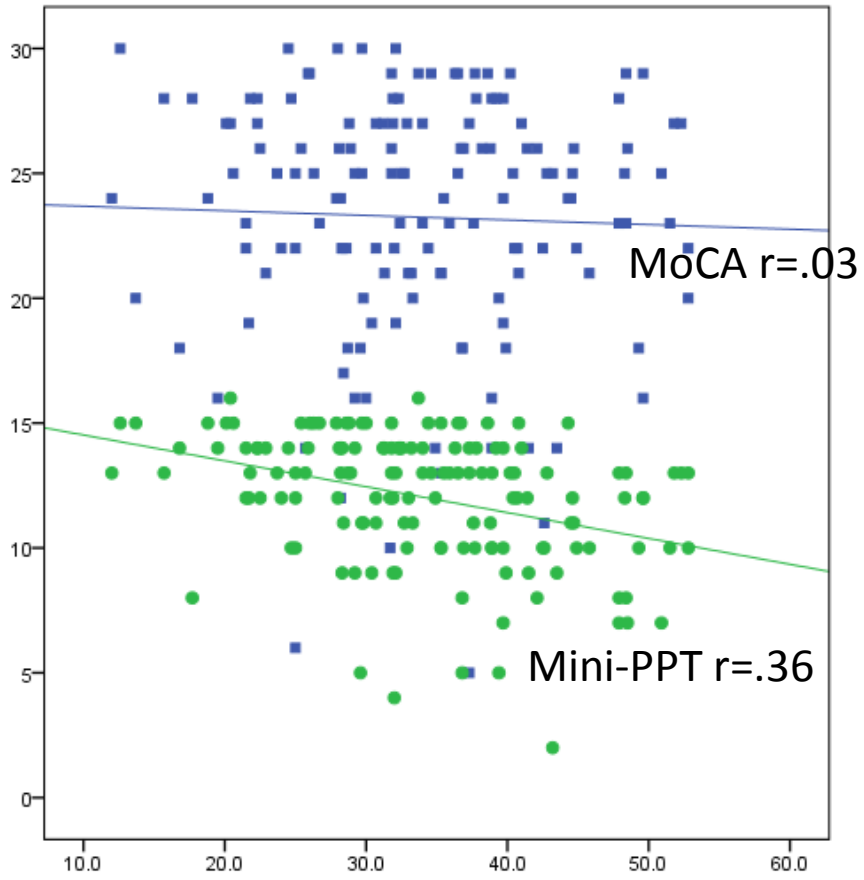
Adjusted Regression Model for Lean BMI

	Exp(B)	95% CI
Age	.968	0.94 – 0.99
Gender	1.23	0.65 – 2.33
Lean BMI	1.00	0.89 – 1.14



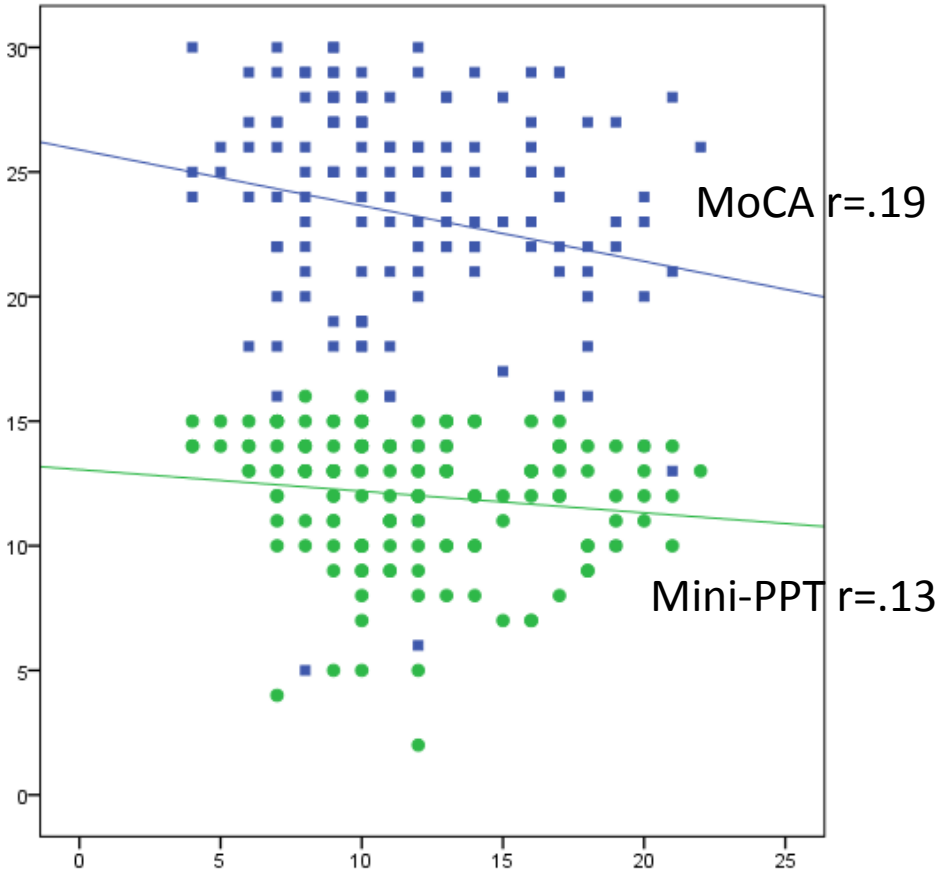
Differences: Visceral and Body Fat

Body Fat



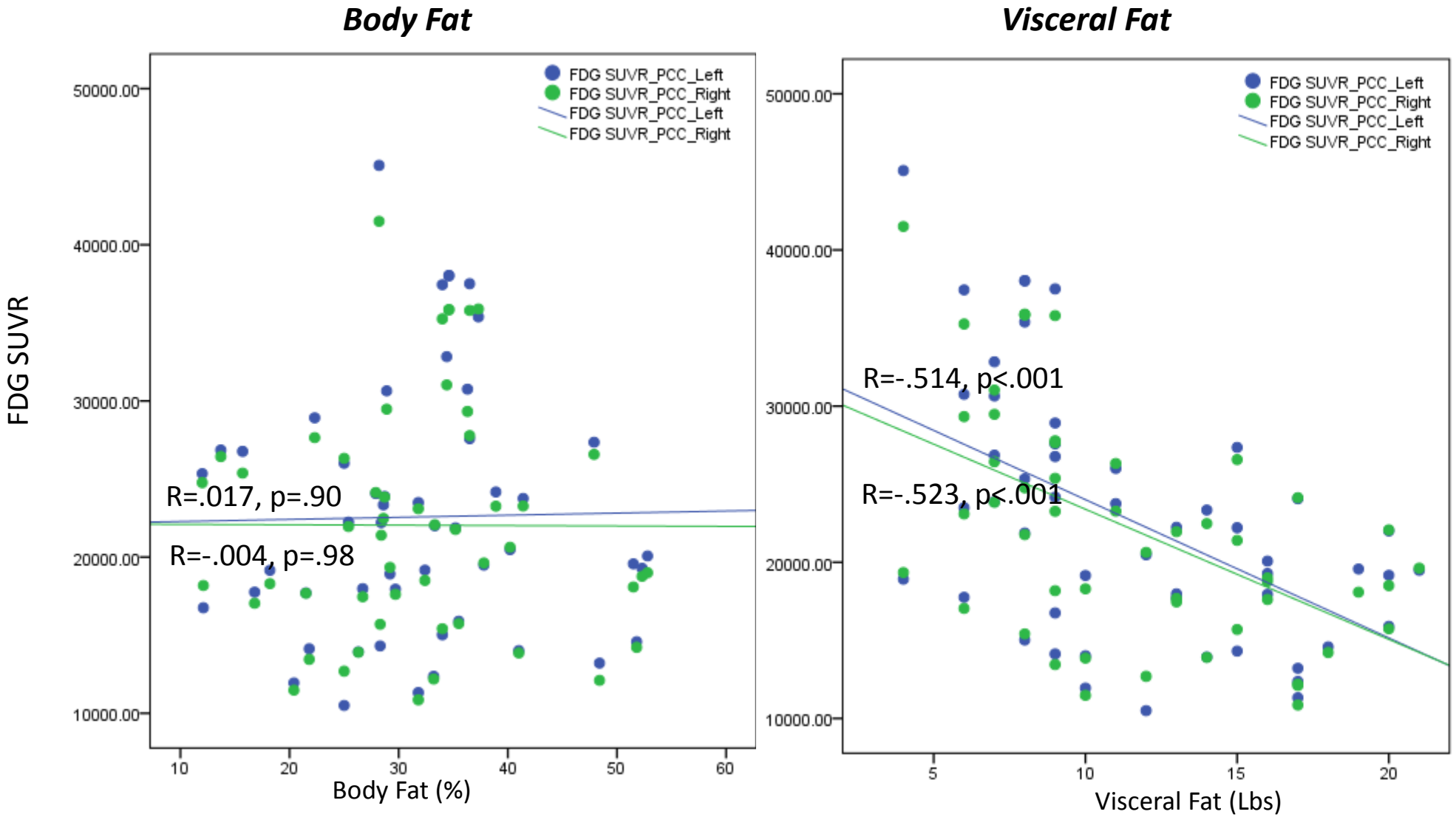
Worse ***Physical*** Performance

Visceral Fat

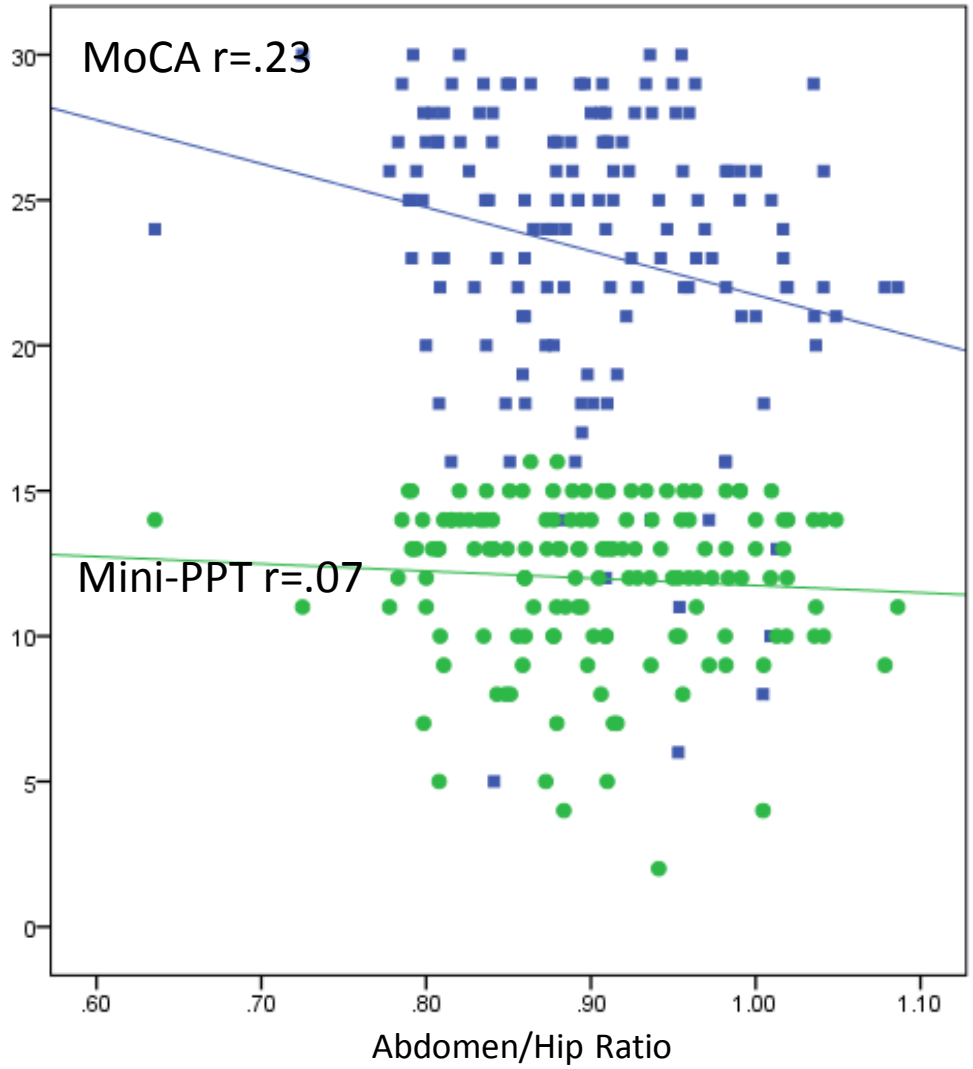


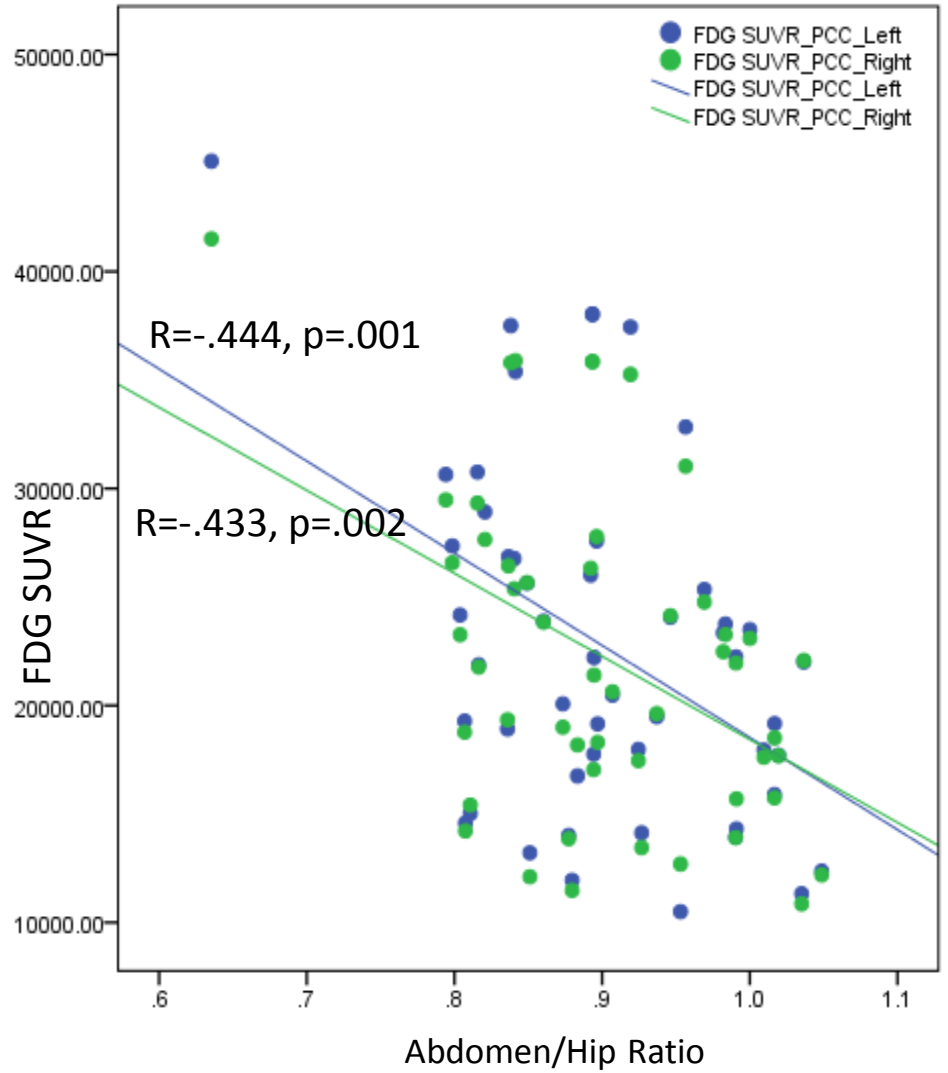
Worse ***Cognitive*** Performance

Differences: Visceral and Body Fat



Abdomen/Hip Ratio as Proxy Marker





Hypertension and risk of AD

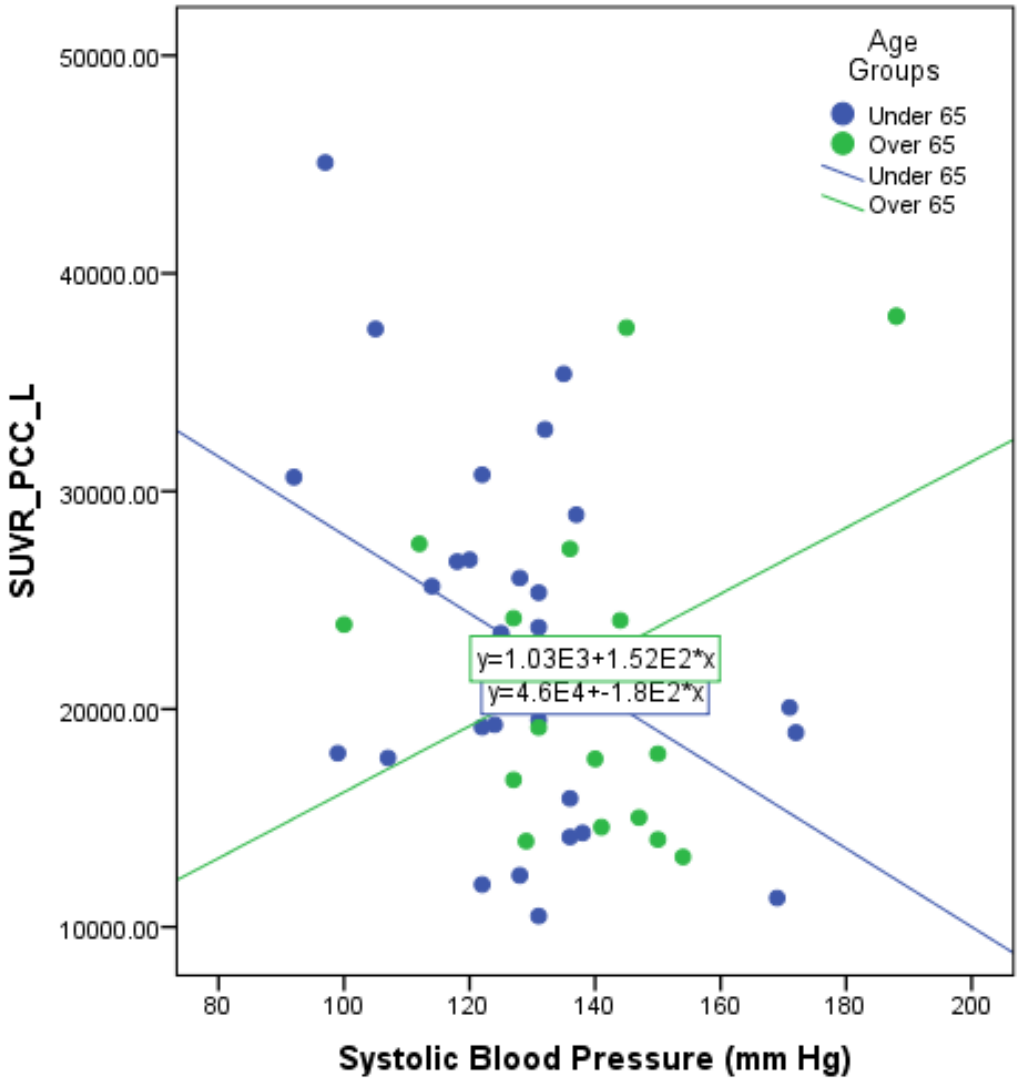
Table 1 | High blood pressure and dementia

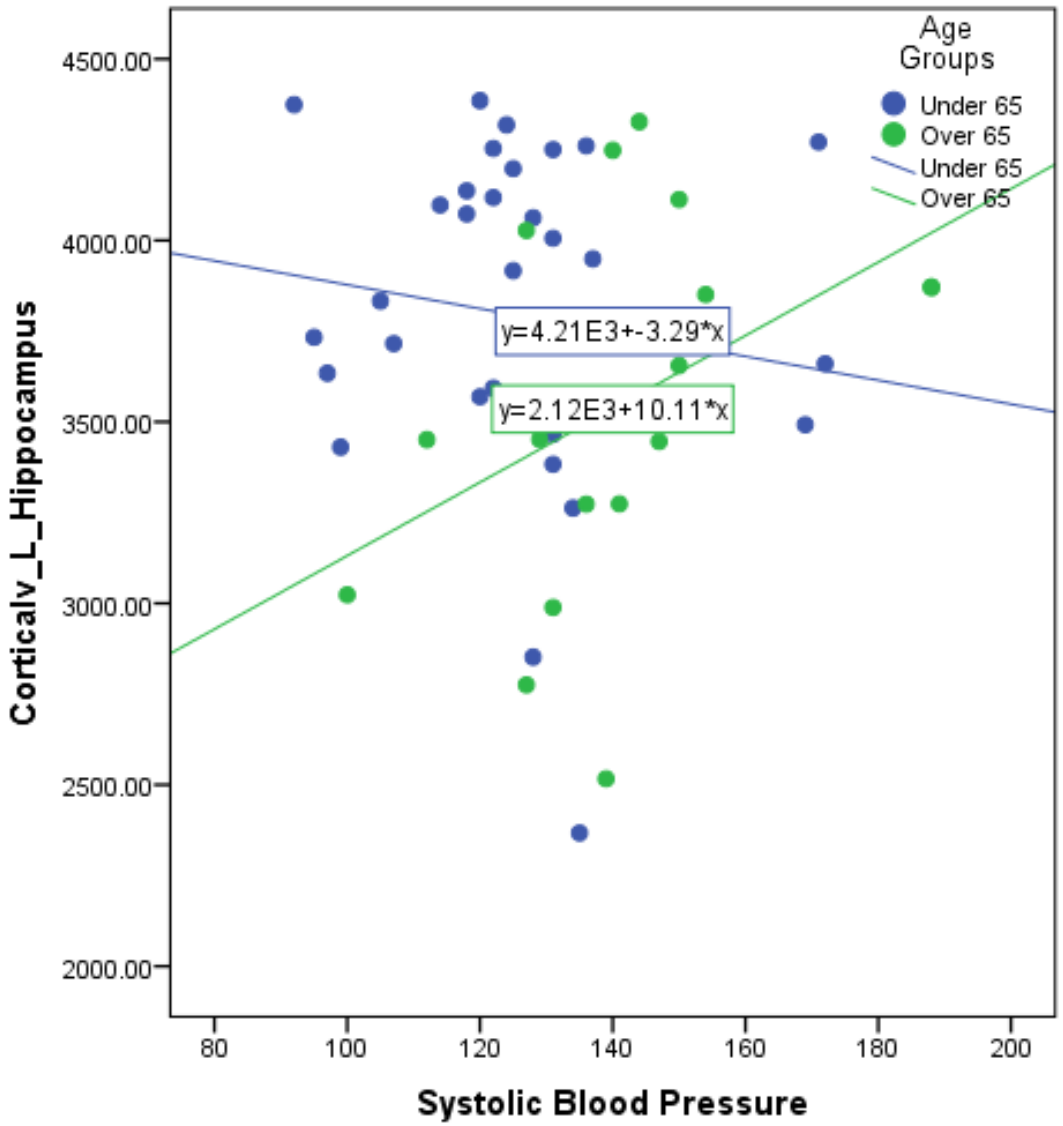
Study	Subjects	Blood pressure classification	Outcome	Follow-up period	Results (odds ratio or relative risk; 95% CI)
Launer *et al.*[19]	3,703 Japanese-American men; never treated hypertensives 57%	DBP; severe high (≥95 mm Hg); high (90–94 mm Hg); normal (80–89 mm Hg), SBP; severe high (≥160 mm Hg); high (140–159 mm Hg); normal (110–139 mm Hg)	Dementia	27 (years)	Among those never treated, the risk for dementia was 3.8 (1.6–8.7) for severe high DBP, and 4.3 (1.7–10.8) for high DBP; the risk for dementia was 4.8 (2.0–11.0) in those with severe high SBP. BP was not associated with the risk for dementia in treated men
Kivipelto *et al.*[20]	1,449 subjects; age 65–79	High SBP ≥ 160 mm Hg	Dementia	21 (years)	The risk for dementia was 2.3 (1.0–5.5) for high SBP
Kivipelto *et al.*[21]	1,449 subjects; age 65–79	High SBP ≥ 160 mm Hg	AD	21 (years)	The risk for AD was 2.6 (1.1–6.6) for high SBP
Posner *et al.*[22]	1,259 subjects; age ≥ 65	N/A	AD, VaD	7 (years)	A history of hypertension was not associated with an increased risk for AD (0.9, 0.7–1.3), but was with an increased risk for VaD (1.8, 1.0–3.2)
Kivipelto *et al.*[23]	1,449 subjects; age 65–79	High SBP > 140 mm Hg	Dementia, AD	21 (years)	High SBP was a significant risk for dementia (1.97, 1.03–3.77); no significant risk for AD (1.57, 0.78–3.14)
Luchsinger *et al.*[24]	1,138 subjects; mean age 76.2	N/A	AD	5.5 (years)	Hypertension was not significantly associated with an increased risk for AD (1.4, 0.9–2.1)
Li *et al.*[25]	2,356 subjects; age ≥ 65	DBP; borderline-high (80–89 mm Hg); normal (<80 mm Hg), SBP; high (≥160 mm Hg); normal (<140 mm Hg)	Dementia	8 (years)	Within the youngest age group (65–74), a greater risk for dementia was found in participants with high SBP (1.60, 1.01–2.55) or borderline-high DBP (1.59, 1.07–2.35) than for those with normal BP

AD, Alzheimer's disease; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; VaD, vascular dementia.

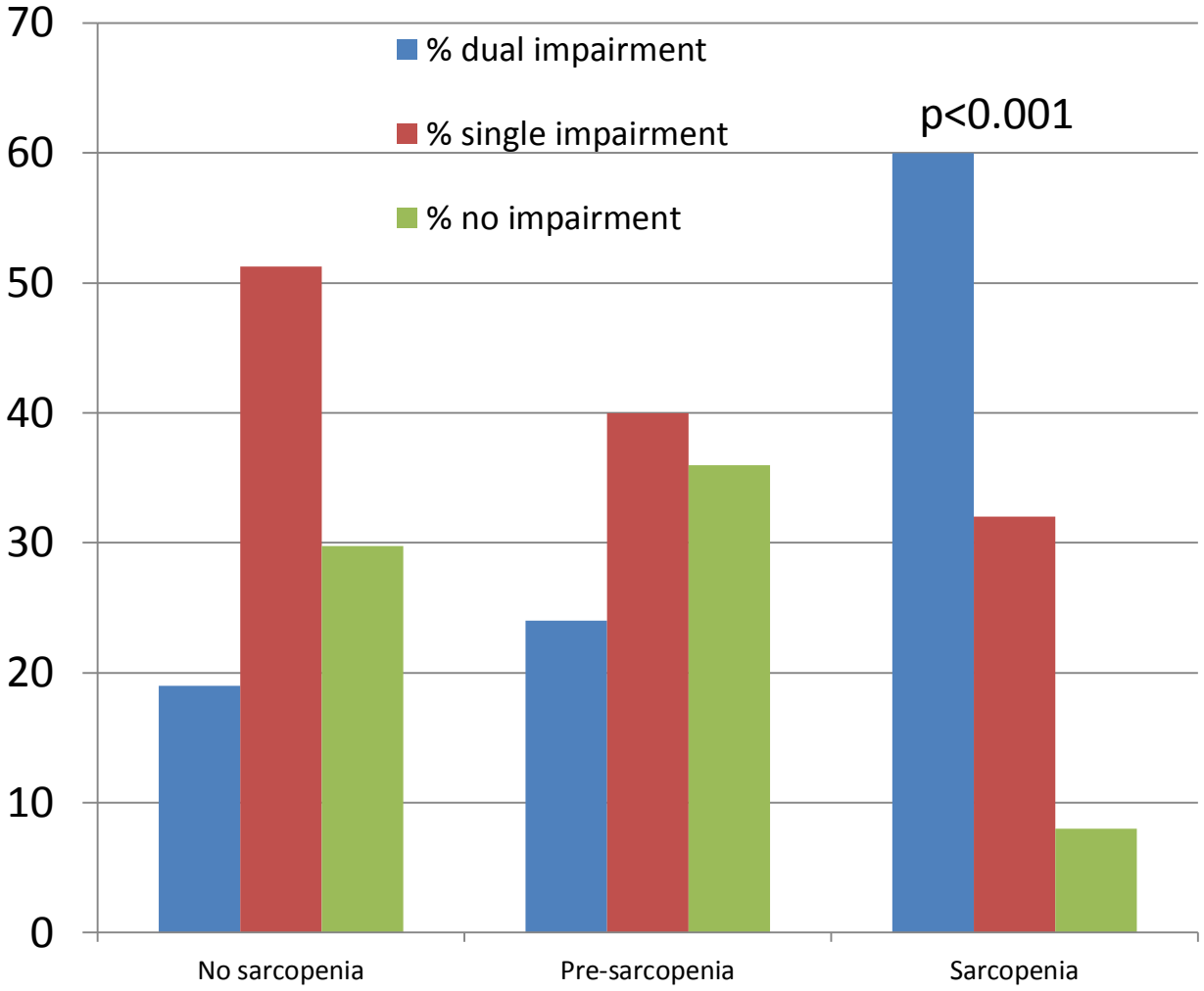
Nagai et al, Am J Hypert 2010

Risk Function of Age





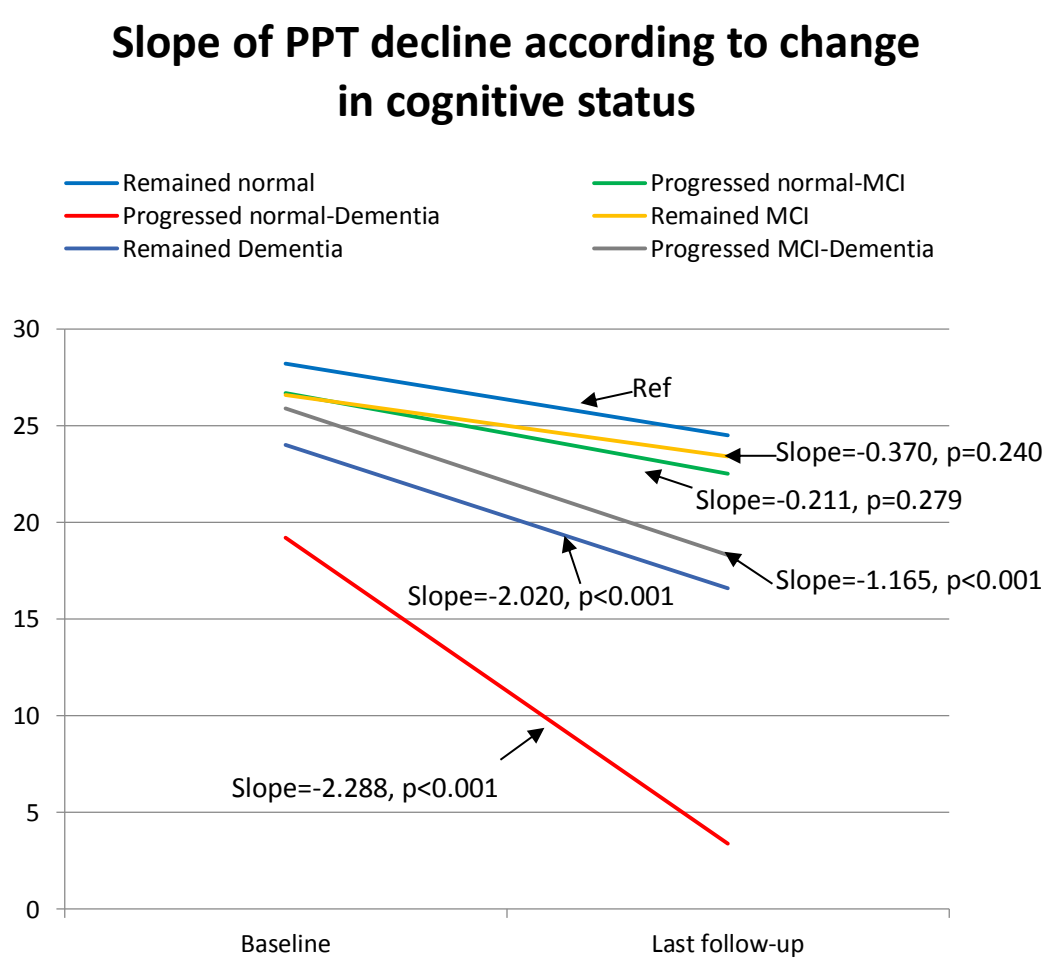
Sarcopenia and Impairment

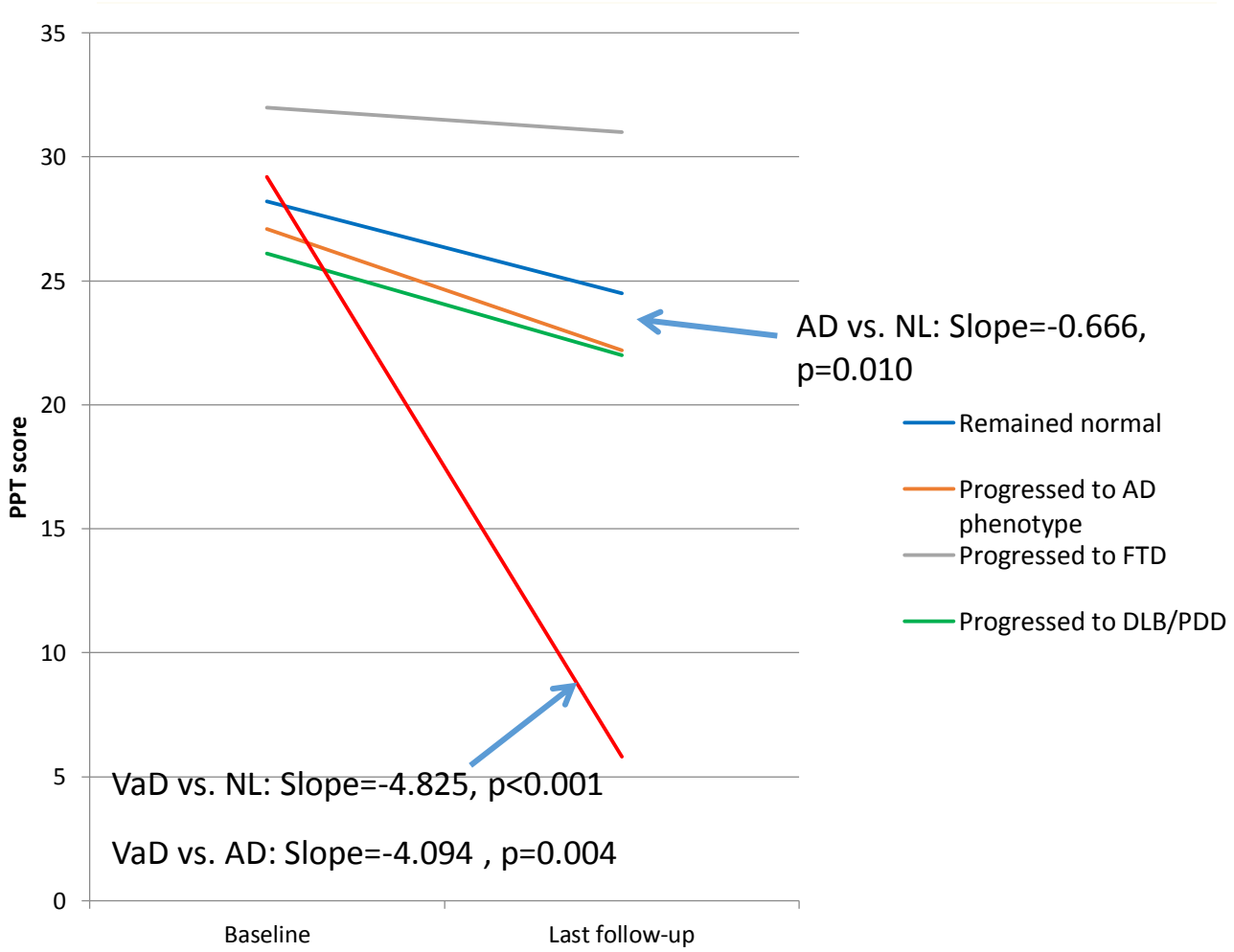


OR of having both cognitive impairment (MoCA) and physical impairment€			
	Unadjusted	Adjusted 1	Adjusted 2
Controls	1.0	1.0	1.0
Pre-sarcopenia	0.90 (0.43-1.94)	1.09 (0.41-3.85)	1.54 (0.54-4.37)
Sarcopenia	**6.02 (2.58-14.33)**	**4.09 (1.40-11.91)**	**3.46 (1.07-11.45)**
OR of having both cognitive impairment (AD8) and physical impairment			
	Unadjusted	Adjusted 1	Adjusted 2
Controls	1.0	1.0	1.0
Pre-sarcopenia	0.93 (0.43-1.99)	0.80 (0.30-2.14)	1.10 (0.37-3.21)
Sarcopenia	**6.10 (2.73-14.07)**	**3.07 (1.09-8.61)**	**3.61 (1.11-11.72)**

Tolea and Galvin, *Clin Intervent Aging, 2014*

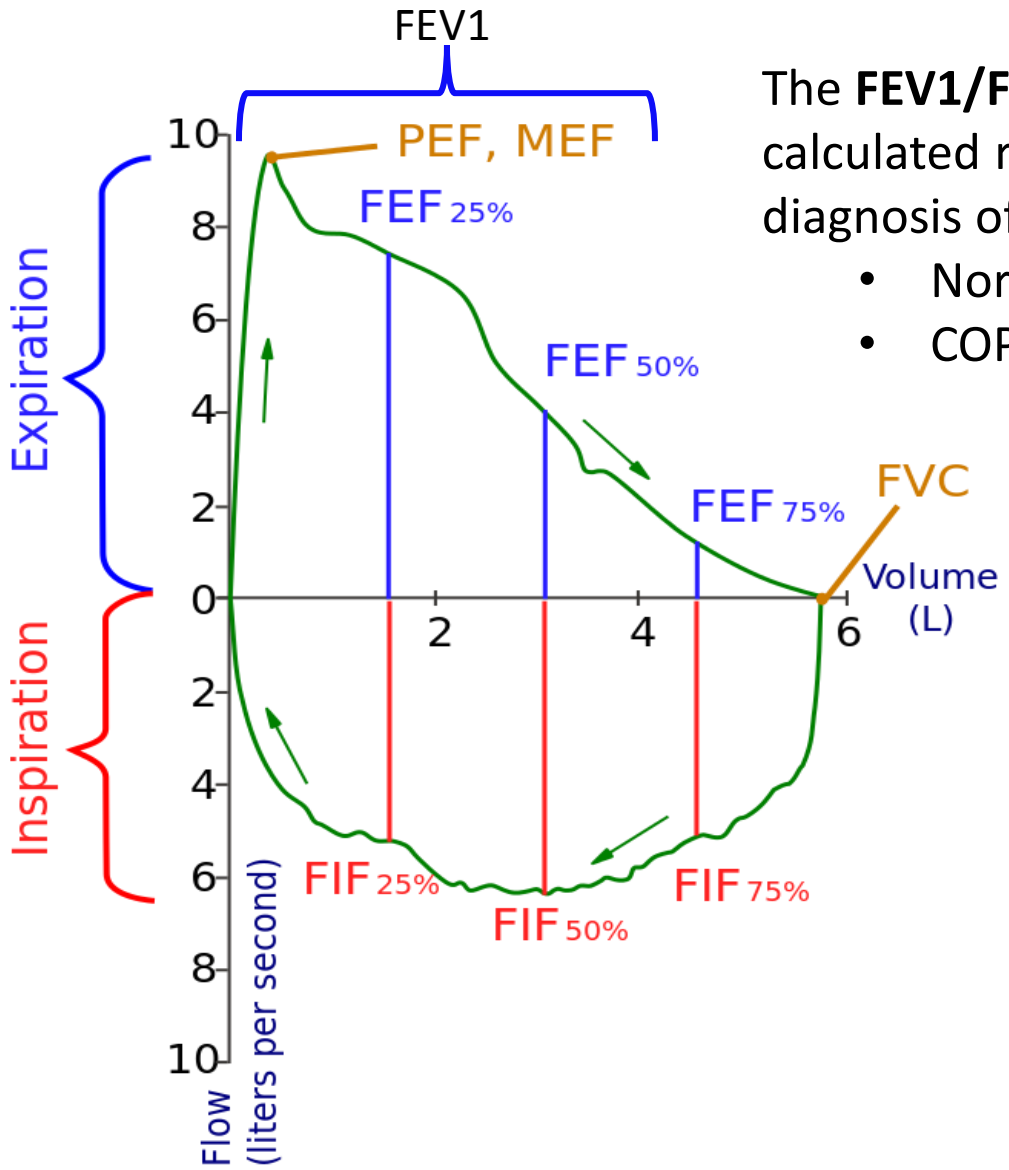
Functional decline depends on initial cognitive status and rate of progression





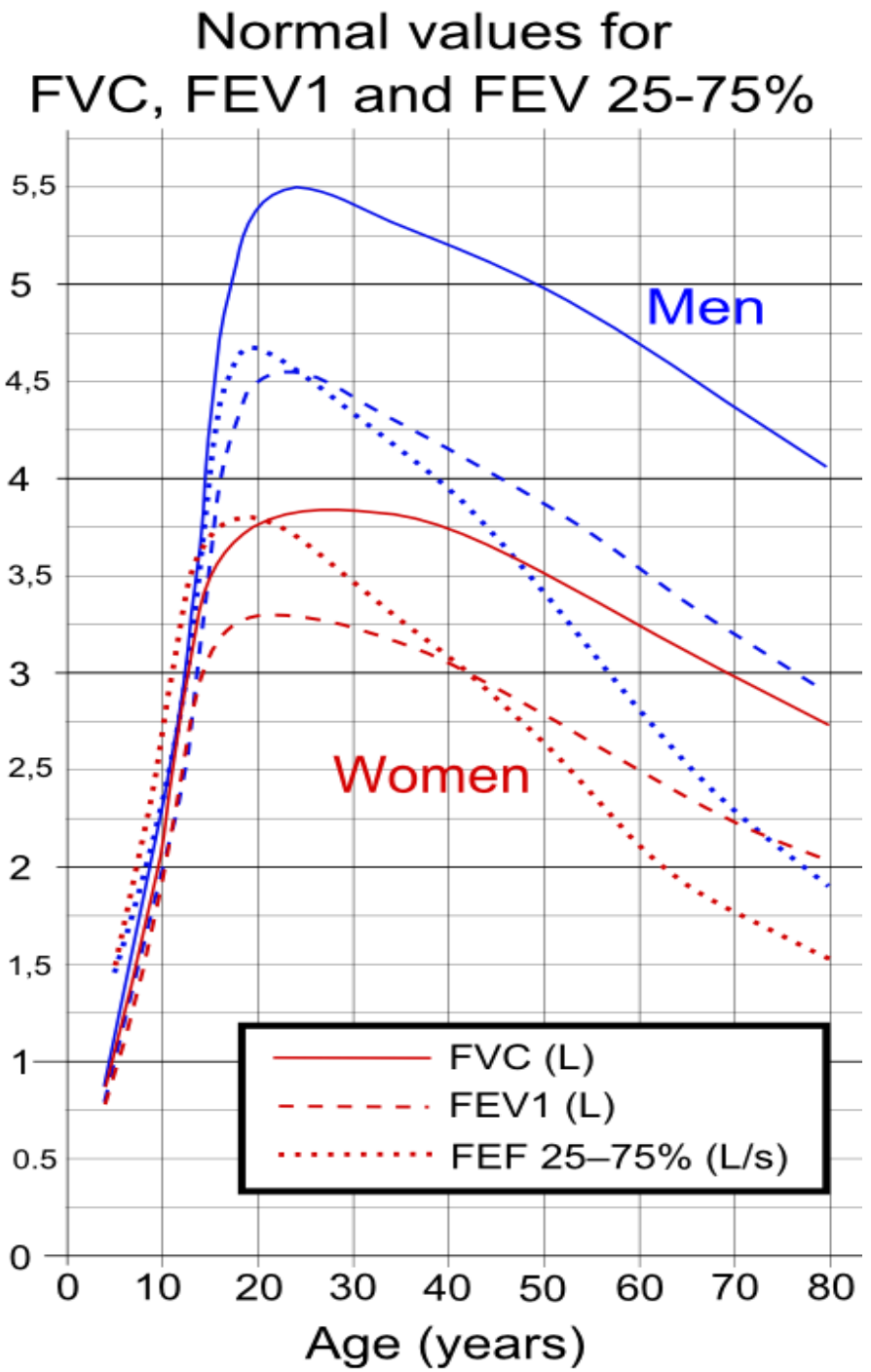
Tolea, Morris and Galvin, *Alz Dis Assoc Disord, 2014*

Lung Volumes



The **FEV1/FVC ratio**, is a calculated ratio used in the diagnosis of COPD

- Normal ≥ 0.8
- COPD < 0.7



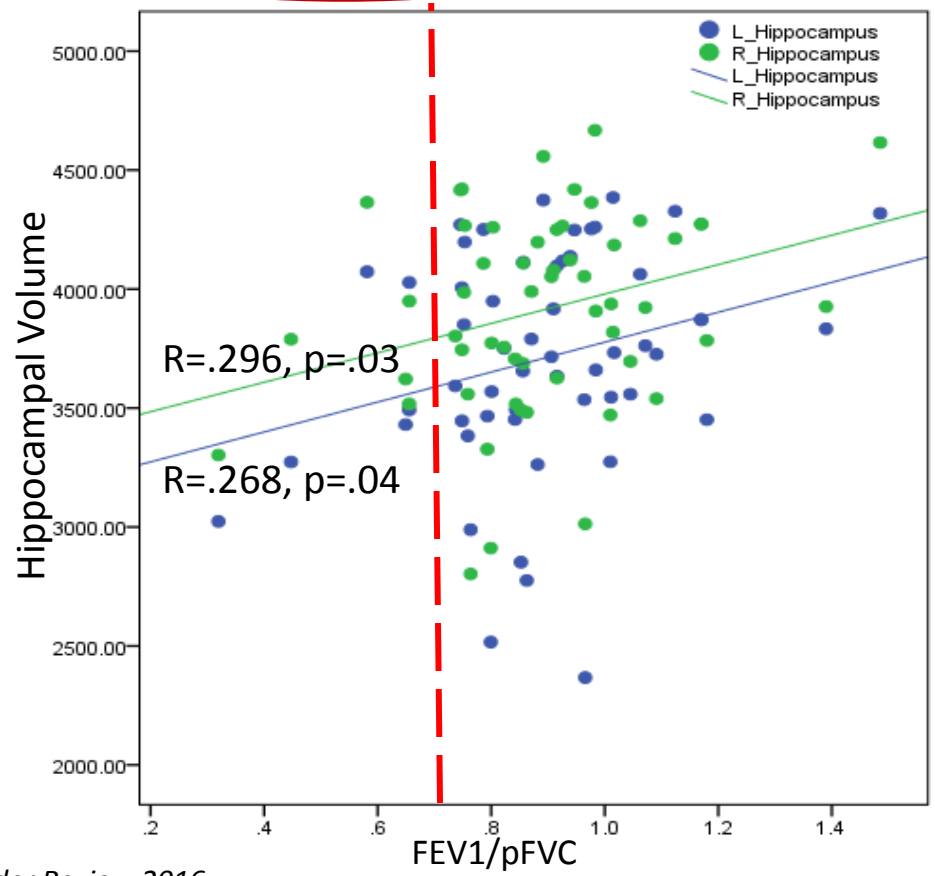
COPD Risk and Cognitive Performance

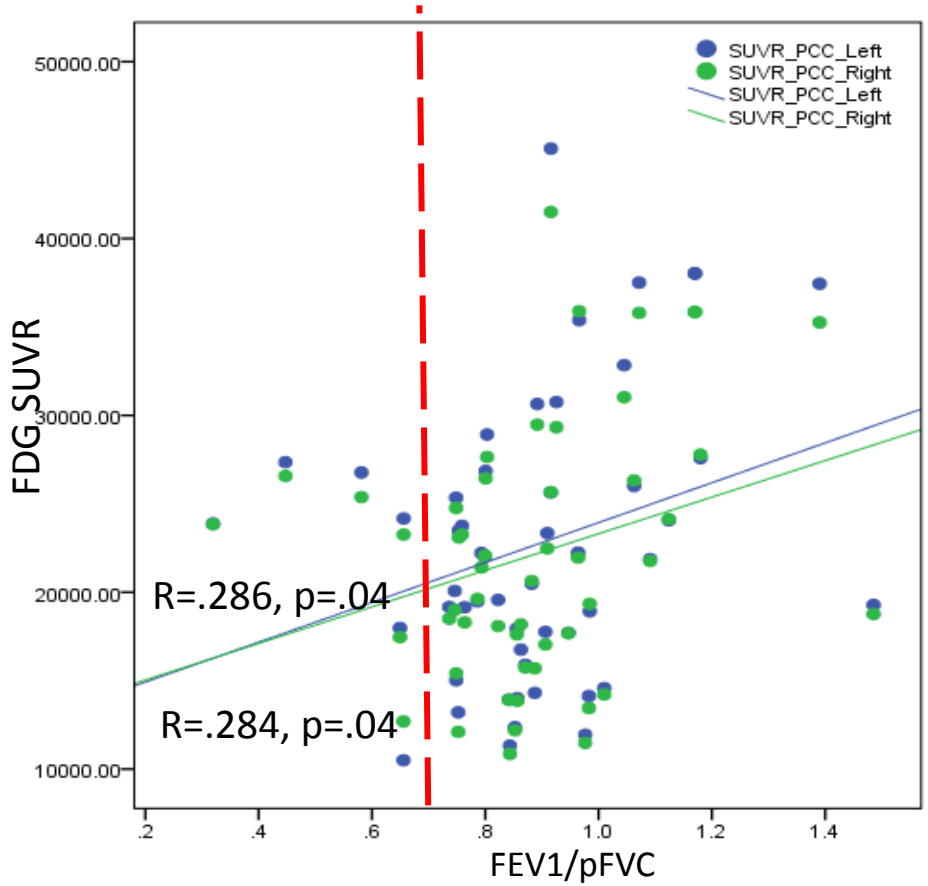
Adjusted Regression Model

	OR	95% CI
Age	1.03	1.00 – 1.06
Gender	0.78	0.43 – 1.44
FEV1/pFVC	8.5	3.1-31.2

	Estimate	Std Error	P-value
Lung Age/Age Ratio	-0.55	0.17	.002

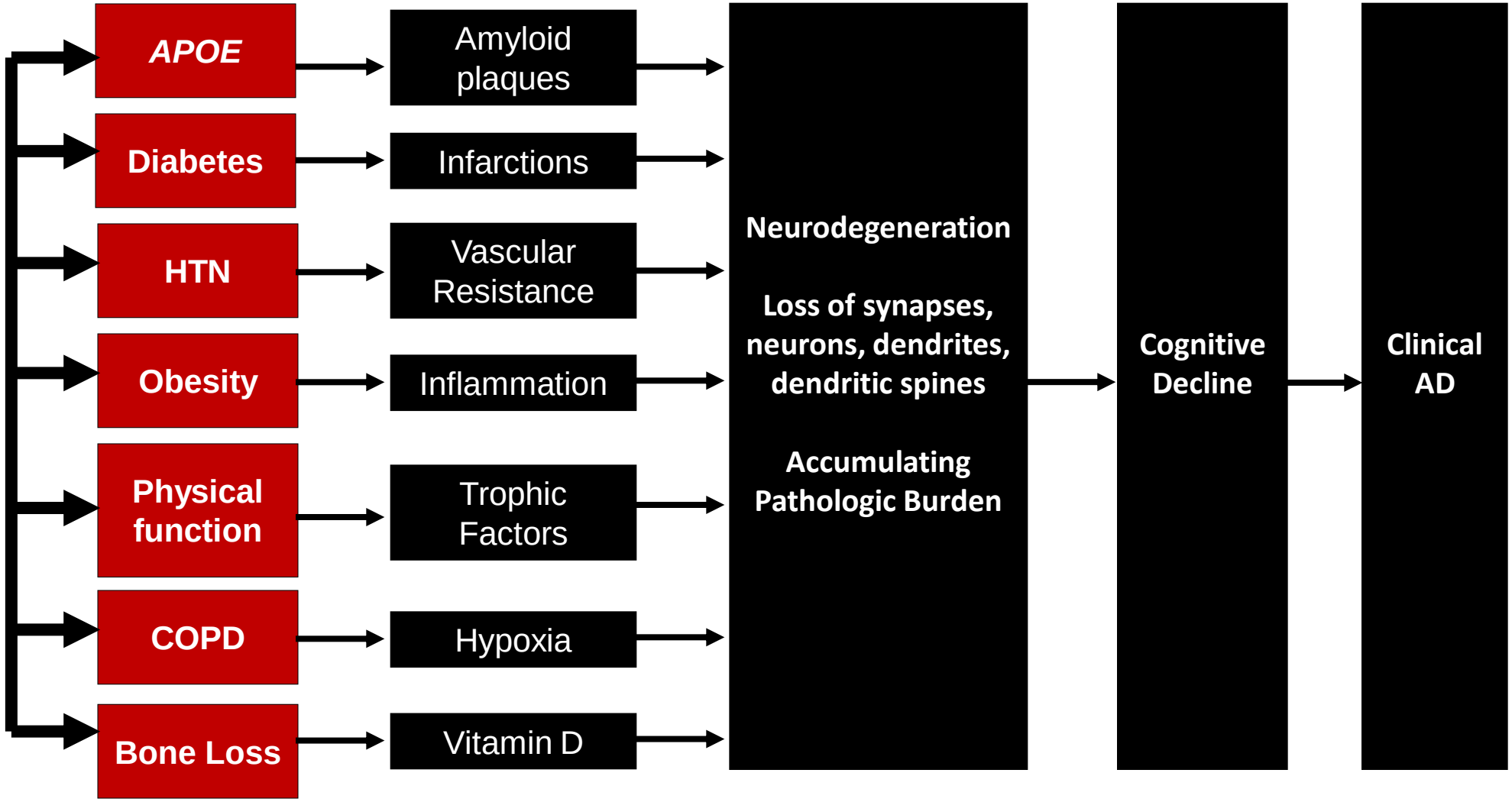
Every 0.5 difference in Lung Age/Chronological Age ratio effects MoCA by 1 point
Risk of poorer cognitive performance: OR 3.95 (95% CI: 1.73-9.09)





Galvin and Tolea, *Under Review 2016*

Clinical Expression of AD Revisited



Dementia Prevention Initiative

- While we cannot (yet) cure AD, there is increasing evidence AD risk is potentially modifiable (HTN, DM, cardiovascular disease, hypercholesterolemia, obesity, etc)

Collective findings identified:

- Specific dietary patterns and nutrient profiles associated increased AD pathology
- Changes in muscle mass, mobility and body fat associated with poorer cognitive performance
- Racial, ethnic and socioeconomic differences in health outcomes, perception, and use of medical information
- Personality profiles that increase physical and cognitive limitations
- Cognitive profiles characterizing preclinical, presymptomatic disease
- Novel cognitive tasks that portend accumulating AD brain pathology
- Brain imaging changes occurring very early in pathologic cascade

Develop individualized risk profile:

- Diet, physical exercise (aerobic, strength training, and flexibility), mental activities, counseling, risk reduction, and homeopathic approaches
- Comprehensive medical history and exam
- Anthropometric measurements
- Novel physical and cognitive tasks
- Dietary and physical activity profiles
- Psychological profile (personality, mood)
- Social support and network assessment
- Blood work for micro- and macro-nutrients, inflammatory/cell injury markers, lipoproteins
- MRI with novel research sequences (volume, surface area, thickness, white matter disease, vascular burden)
- CSF biomarkers of amyloid, tau, inflammation, and neuron injury

- ***Hypothesis:*** Personalized prevention plan alters pathologic cascade in at-risk individuals
- Test tailored intervention over 3-year period to determine if personalized prevention plan can reduce dementia risk by altering biophysiological profiles and biomarkers

Falls Prevention Program

Patient Referral

ADAC

ADAC Assessment
Family sees: 1. MD; 2. SW
Patient sees: 1. SW; 2. NP; 3. MD

CLINIC

Diagnostic Conference
Dyad sees entire team

C-PROFET

Director: JE Galvin
Steering Committee

Eligibility
NP

Informed Consent
Coordinator

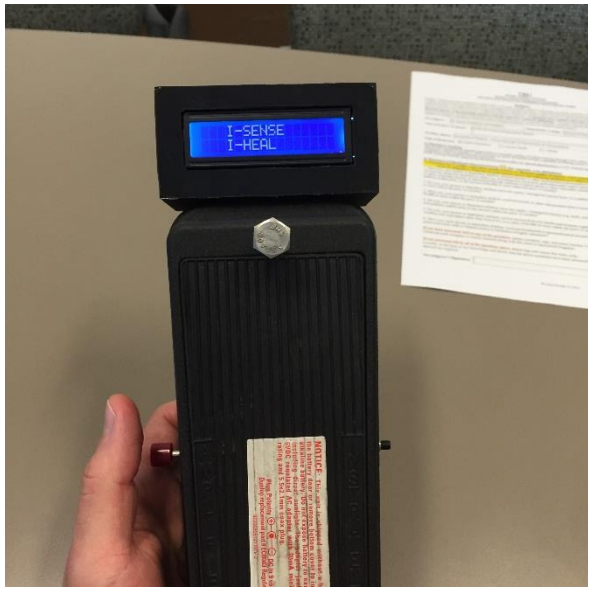
Home visit
1. OT
2. RA

Questions
Medical = NP
Falls prevention = OT

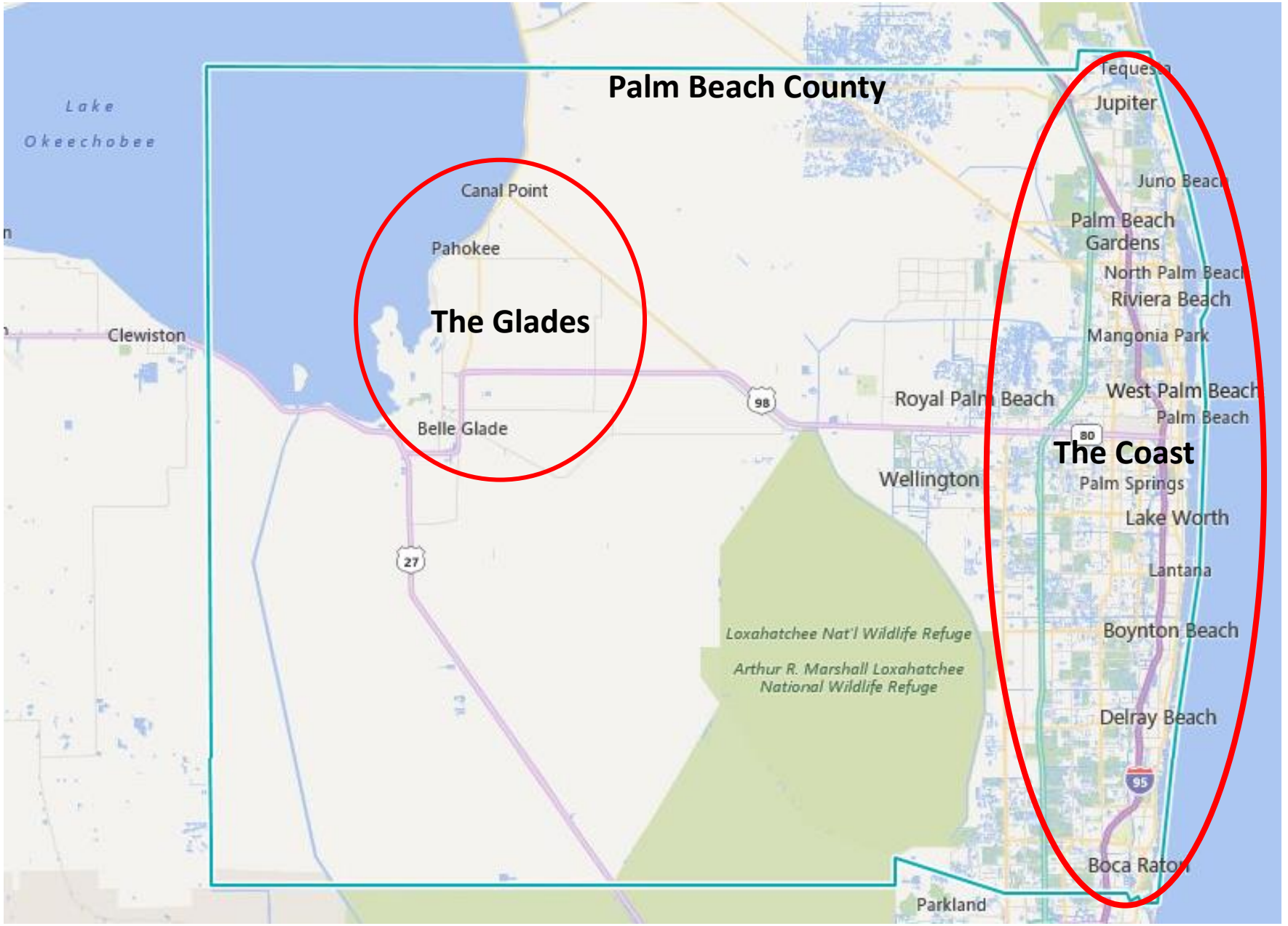
In-Person Follow-ups
1. NP
2. Coordinator

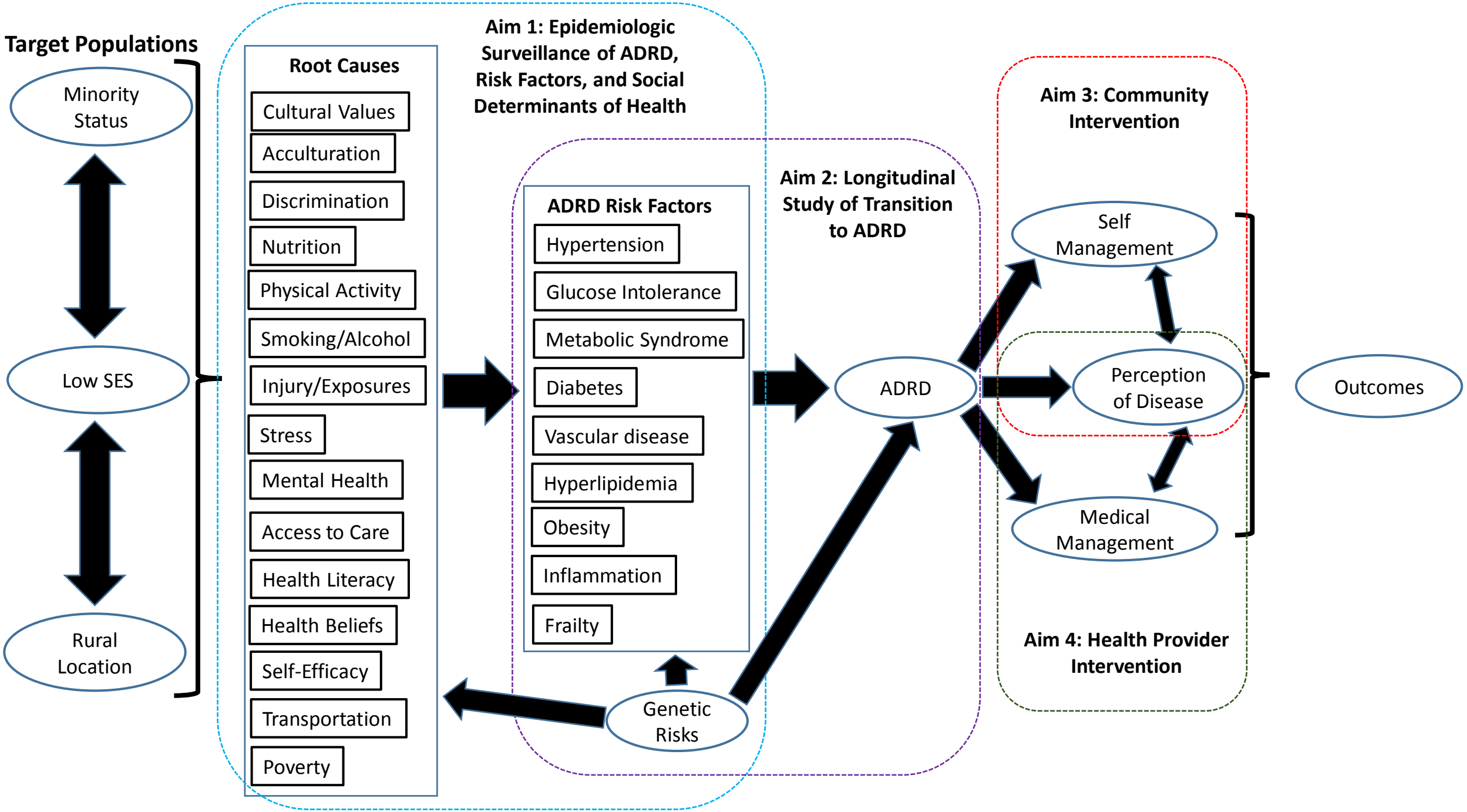
Phone Follow-ups
1. Coordinator
2. RA

Collaboration with I-SENSE to build external sensor devices



New Initiative




Target Populations
Minority Status
Low SES
Rural Location
Root Causes
Cultural Values
Acculturation
Discrimination
Nutrition
Physical Activity
Smoking/Alcohol
Injury/Exposures
Stress
Mental Health
Access to Care
Health Literacy
Health Beliefs
Self-Efficacy
Transportation
Poverty
Aim 1: Epidemiologic Surveillance of ADRD, Risk Factors, and Social Determinants of Health
ADRD Risk Factors
Hypertension
Glucose Intolerance
Metabolic Syndrome
Diabetes
Vascular disease
Hyperlipidemia
Obesity
Inflammation
Frailty
Aim 2: Longitudinal Study of Transition to ADRD
Genetic Risks
ADRD
Aim 3: Community Intervention
Self Management
Perception of Disease
Medical Management
Aim 4: Health Provider Intervention
Outcomes

Summary

- Multiple medical conditions increase the risk of neurodegeneration
  - May be multiple pathways to get Alzheimer's, Parkinson's, and related disorders
  - May also be multiple pathways to diagnose, treat, cure or prevent
- Efforts to prevent cognitive decline and development of dementia may be more successful when directed to at at-risk individuals based on their physical functional profile
- Detection of and interventions addressing root causes may offer novel approaches to diagnosing, treating, curing, or preventing Alzheimer's and Parkinson's disease
- AD and PD are diseases of a lifetime; there may be many ways to build a better brain as we age
- At FAU, we are spearheading game-changing approaches to improve the lives of our patients and their families

"An Ounce of Prevention is Worth a Pound of Cure"

- Benjamin Franklin