Prevention of Dementia: Update in Evidence-based Approaches for Physicians

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RESEARCH FAMILY CARE EDUCATION

RUSH UNIVERSITY

MINISTRARE PER SCIENTIAM

CHICAGO 1972

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Epidemiology and Patient Oriented Research Sections

Memory Clinic

The Rush **Heart** Center for Women

The CEERIAS Study – Investigative Team

The ATRI- A4 Investigative Team

The API -Generation Investigative Team

The MIND Study Investigative Team

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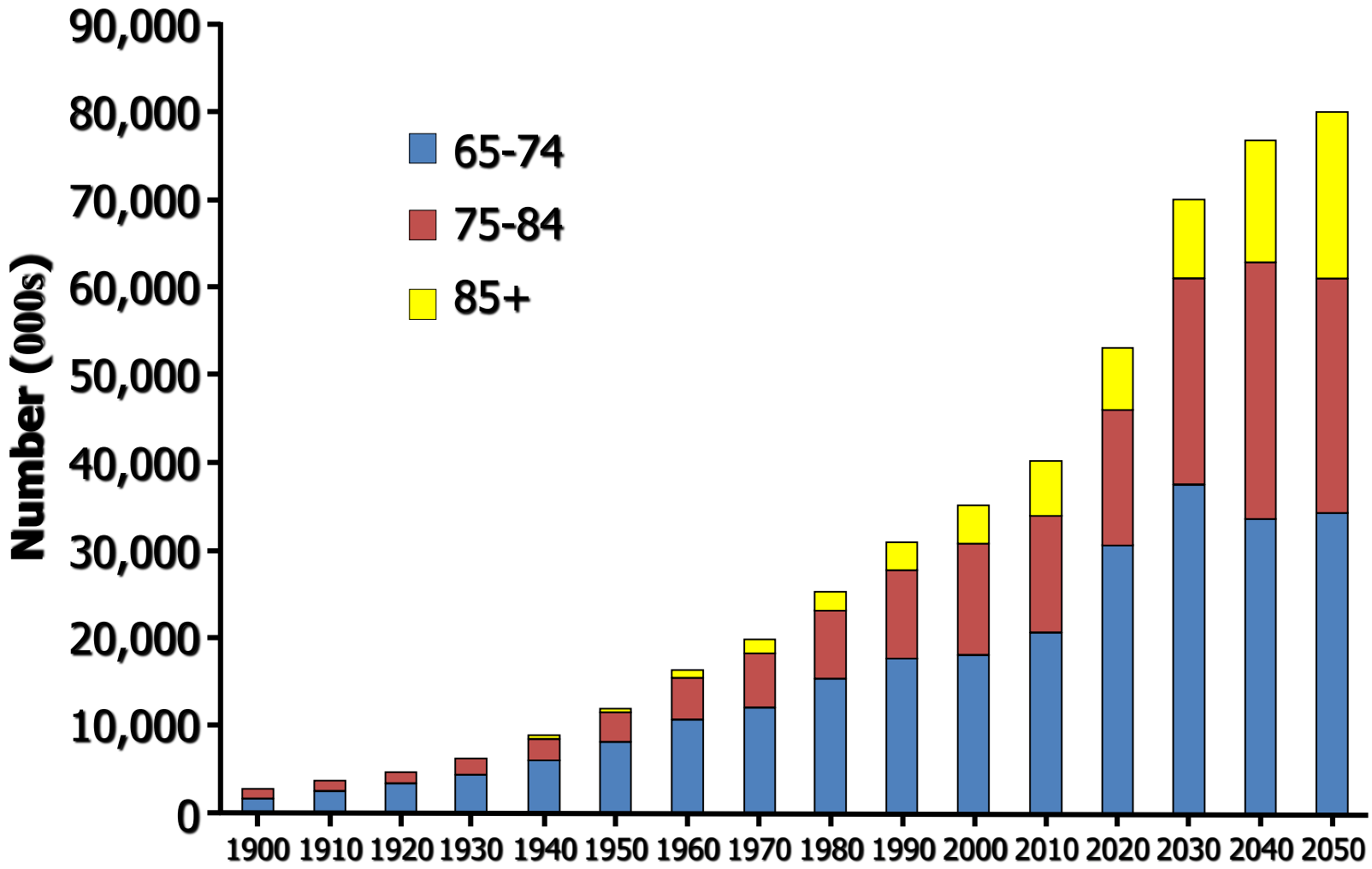
Learning Objectives

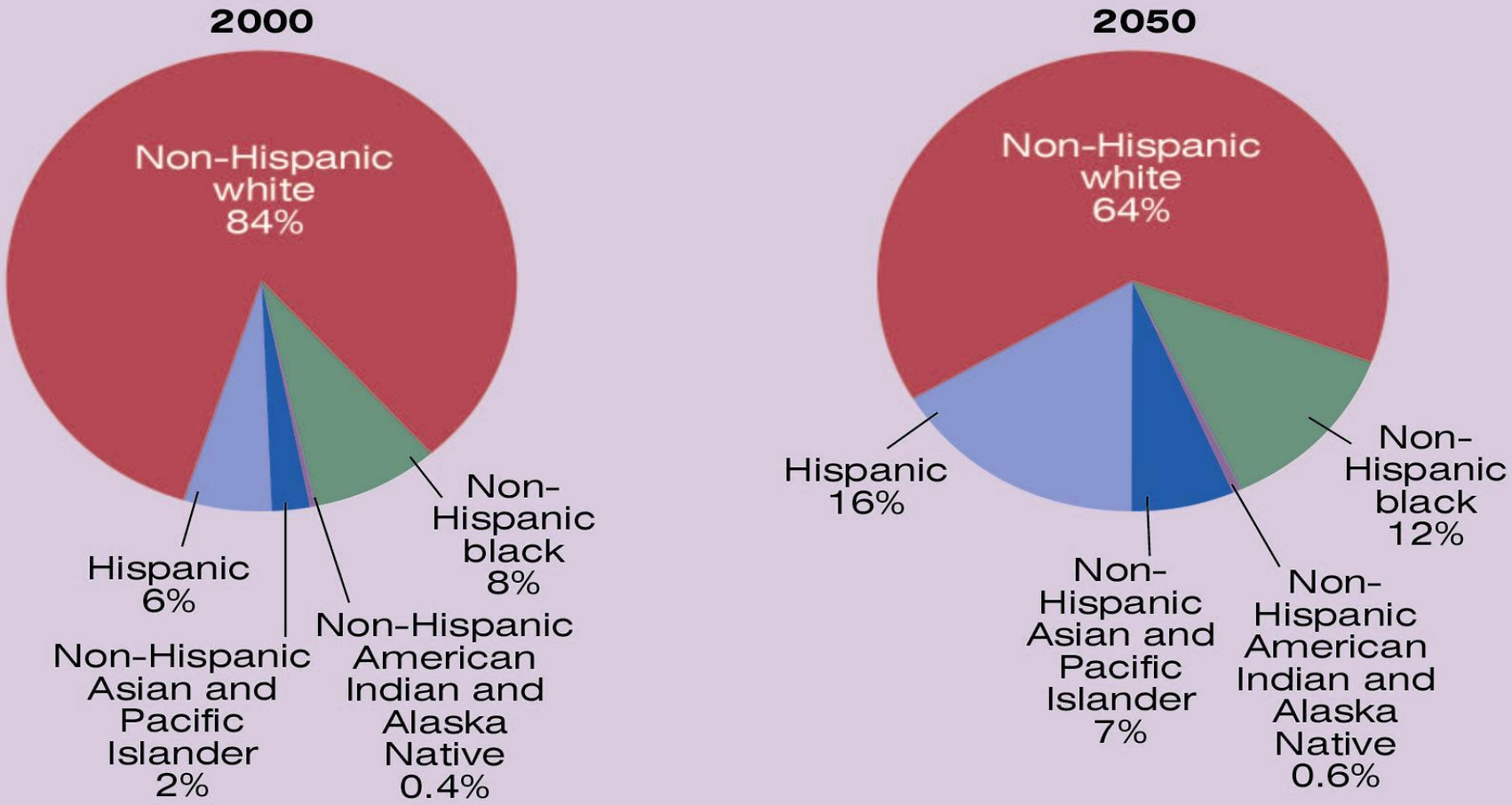
- Review the importance of existing and novel risk factors to cognitive impairment, dementia and Alzheimer's Disease
- Understand the current data surrounding the Heart Brain Connection to Cognitive health and Alzheimer's Disease
- Have greater competence related to the selection of appropriate screening and therapies for the treatment of Alzheimer's Disease (AD) symptoms
- Understand the Emerging Role of Clinical Trials in the Treatment and Prevention of AD

Number of Persons Over 65yrs in US



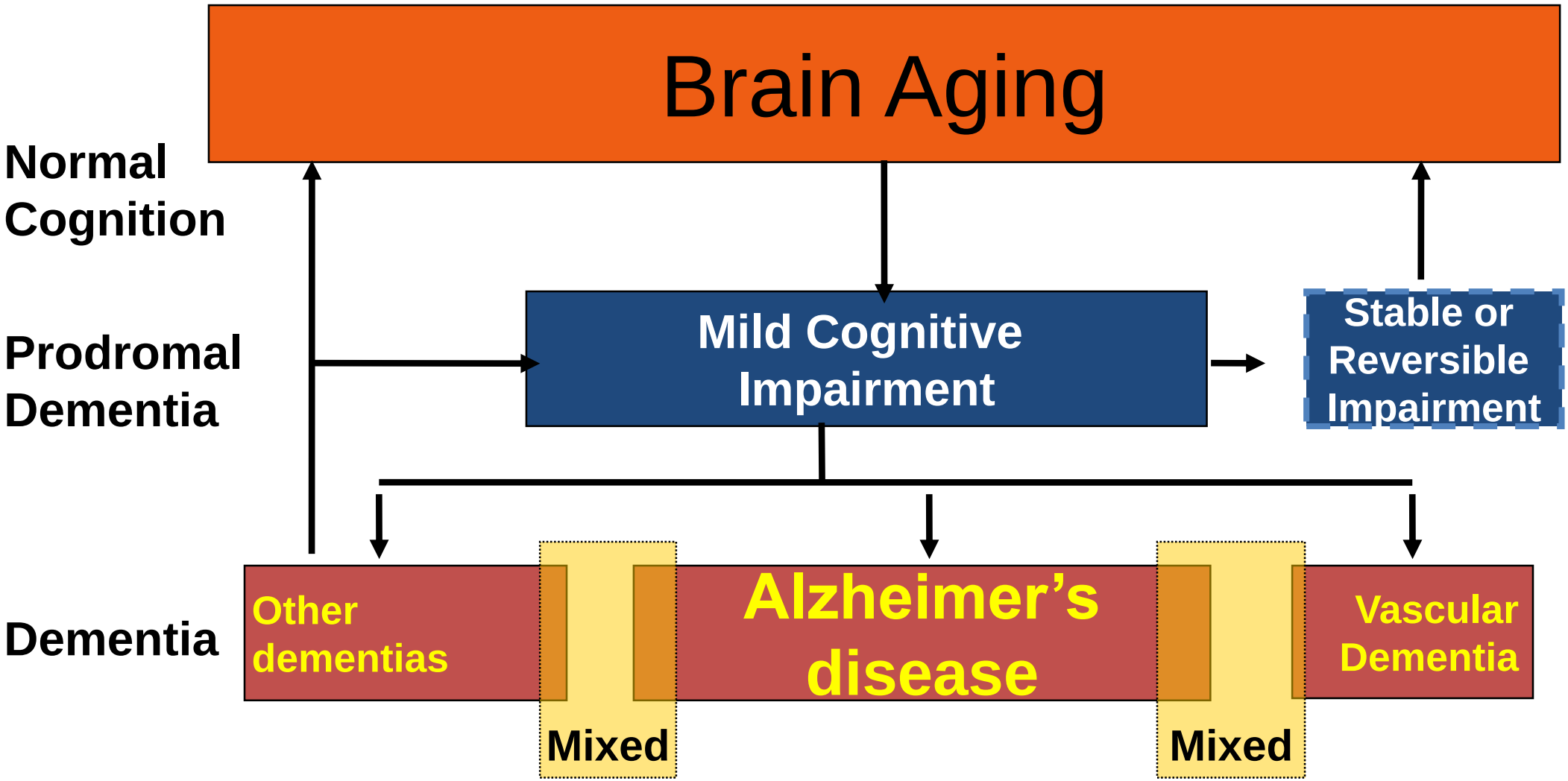
Distribution of Older Adults by Race and Ethnicity

Projected distribution of the population age 65 and older, by race and Hispanic origin, 2000 and 2050



Note: Data are middle-series projections of the population. Hispanics may be of any race.
Reference Population: These data refer to the resident population.
Source: U.S. Census Bureau, Population Projections.

Conceptual Framework of Cognition, Decline and Dementia



Golomb, Kluger, Ferris NeuroScience News, 2000

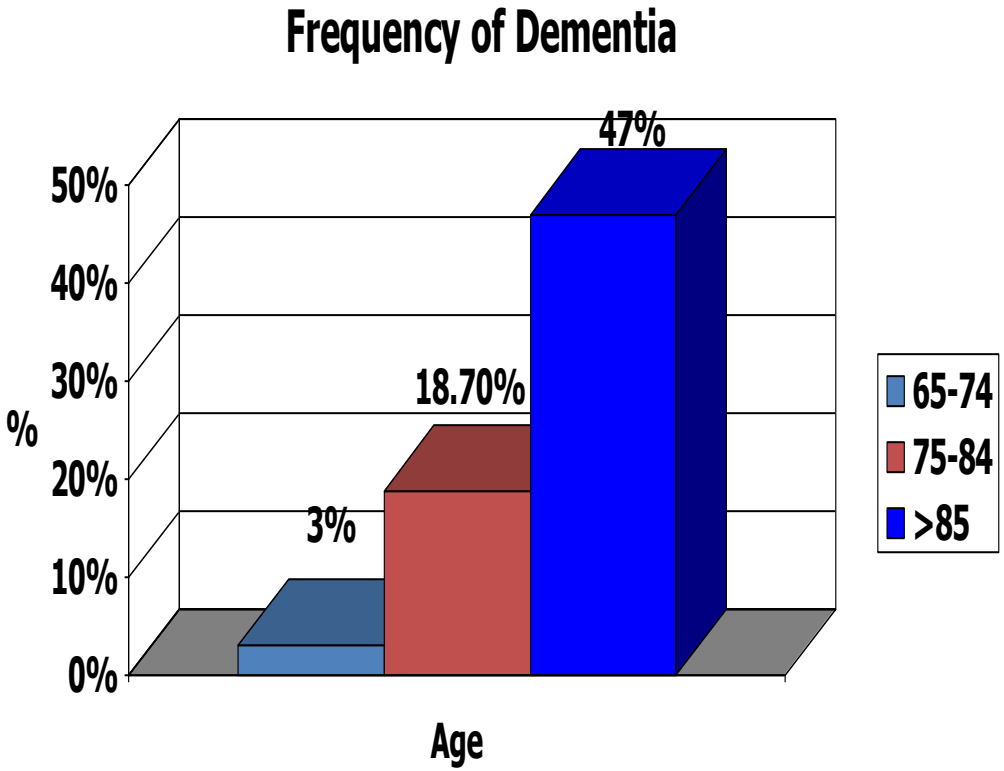
Dementia

General Definition: Medical syndrome of global intellectual decline in multiple domains (atleast 2):

- Memory * Short term- Typically the first sx in AD
- Calculation
- Visual spatial and praxis
- Executive function and judgment
- Language
- Orientation

Activities of daily living must be impaired

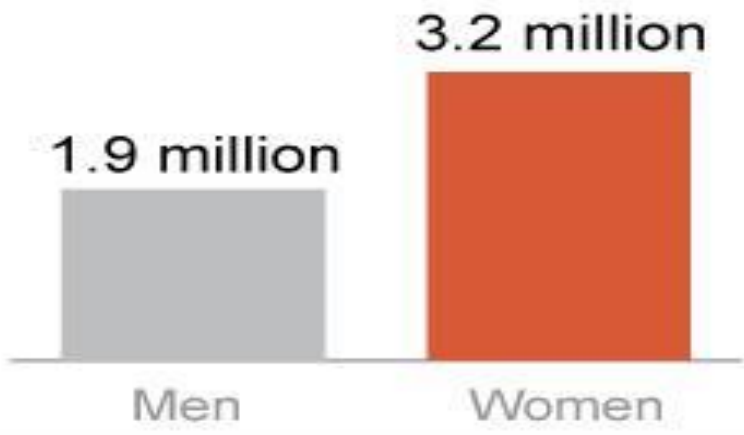
Epidemiology of Dementia



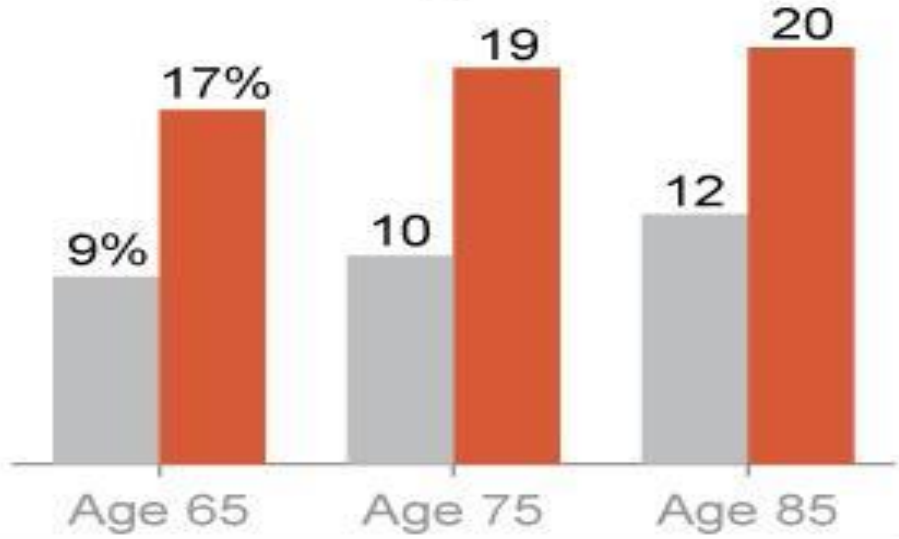
Gender and Alzheimer's disease

Women make up a larger share of Alzheimer's patients than men and have a greater risk of developing the disease as they age.

Number of people ages 65 and older in the U.S. with Alzheimer's:



Percent chance a person will develop Alzheimer's during his or her remaining lifetime:

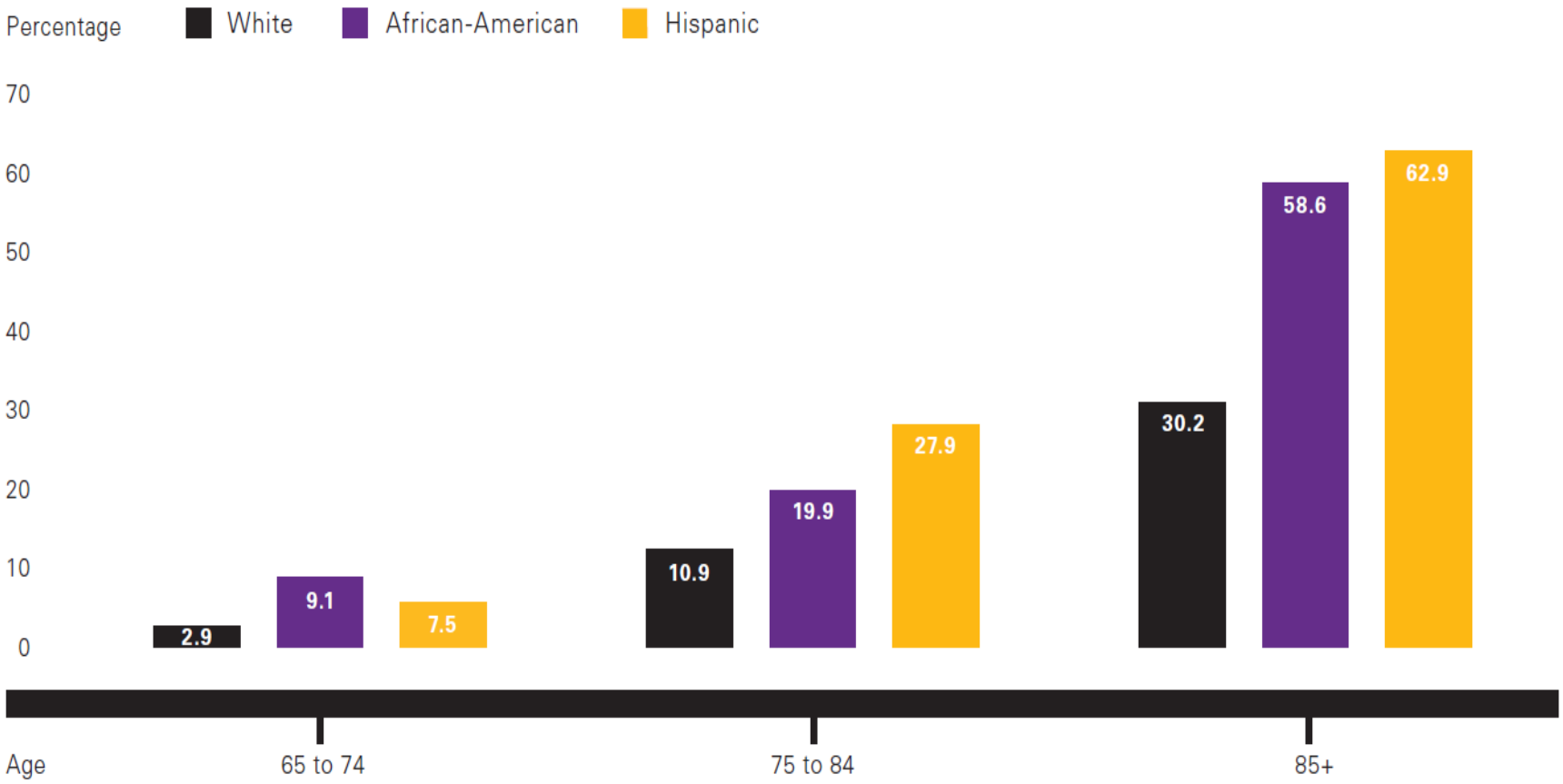


SOURCE: Alzheimer's Association

AP

Race and Ethnicity

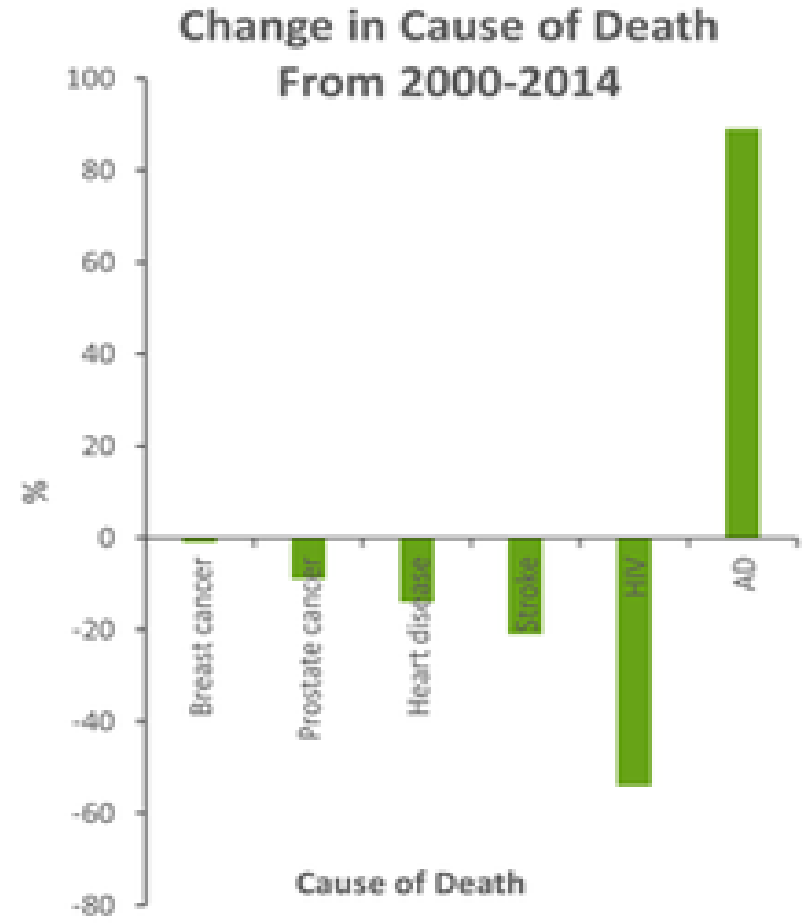
figure 1: Proportion of People Aged 65 and Older with Alzheimer's Disease and Other Dementias, by Race/Ethnicity, Washington Heights-Inwood Columbia Aging Project, 2006



Created from data from Gurland et al. [55]

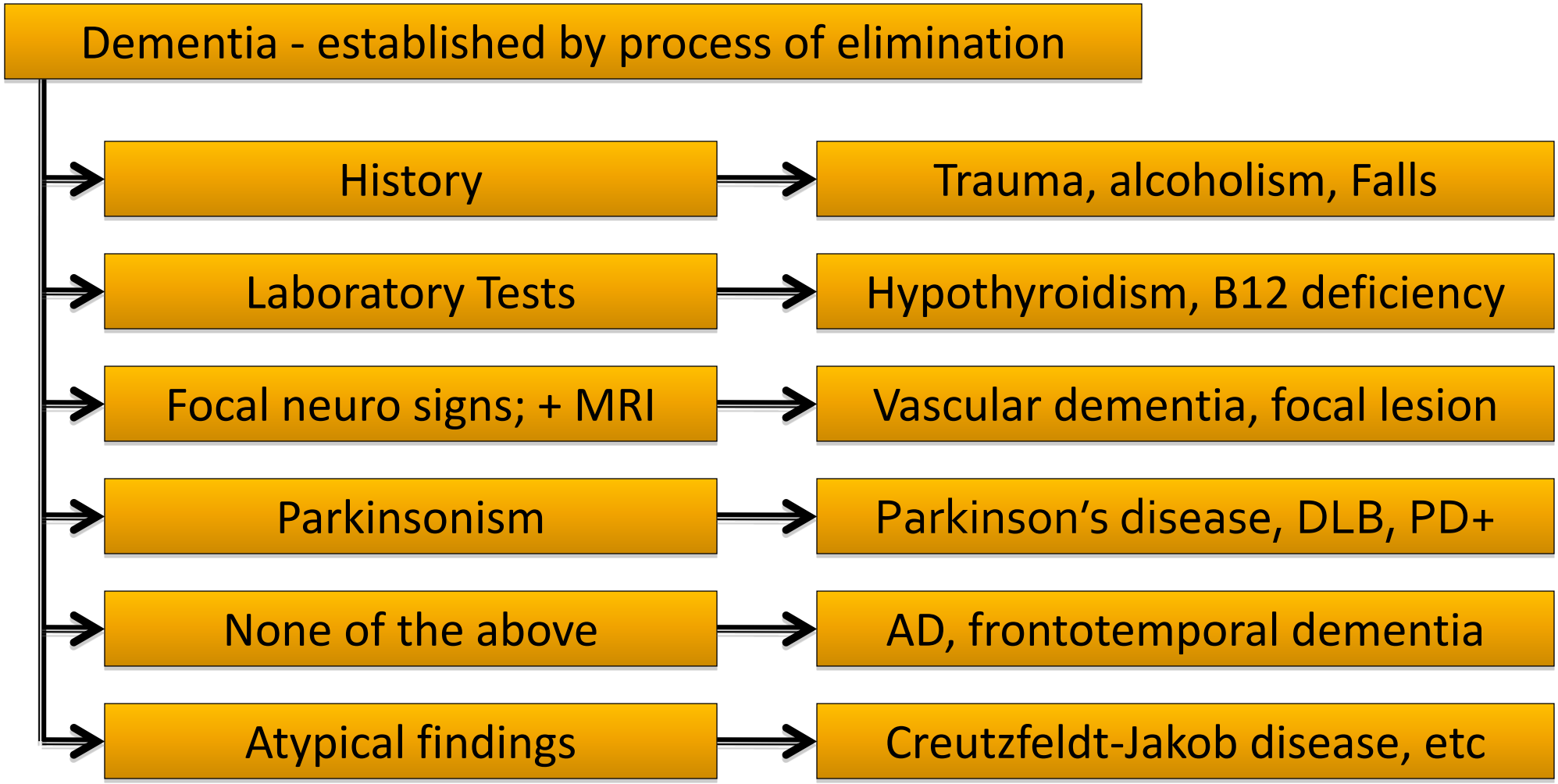
Deaths Attributable to AD in the United States

- 6th leading cause overall
- 5th leading cause in people aged ≥65 years
- In 2017, ~700,000 people aged ≥65 years will have AD when they die, and yet death rates are likely underreported because of underrecognition and other factors
- Only cause of death among the top 10 without a way to prevent, cure, or even slow its progression



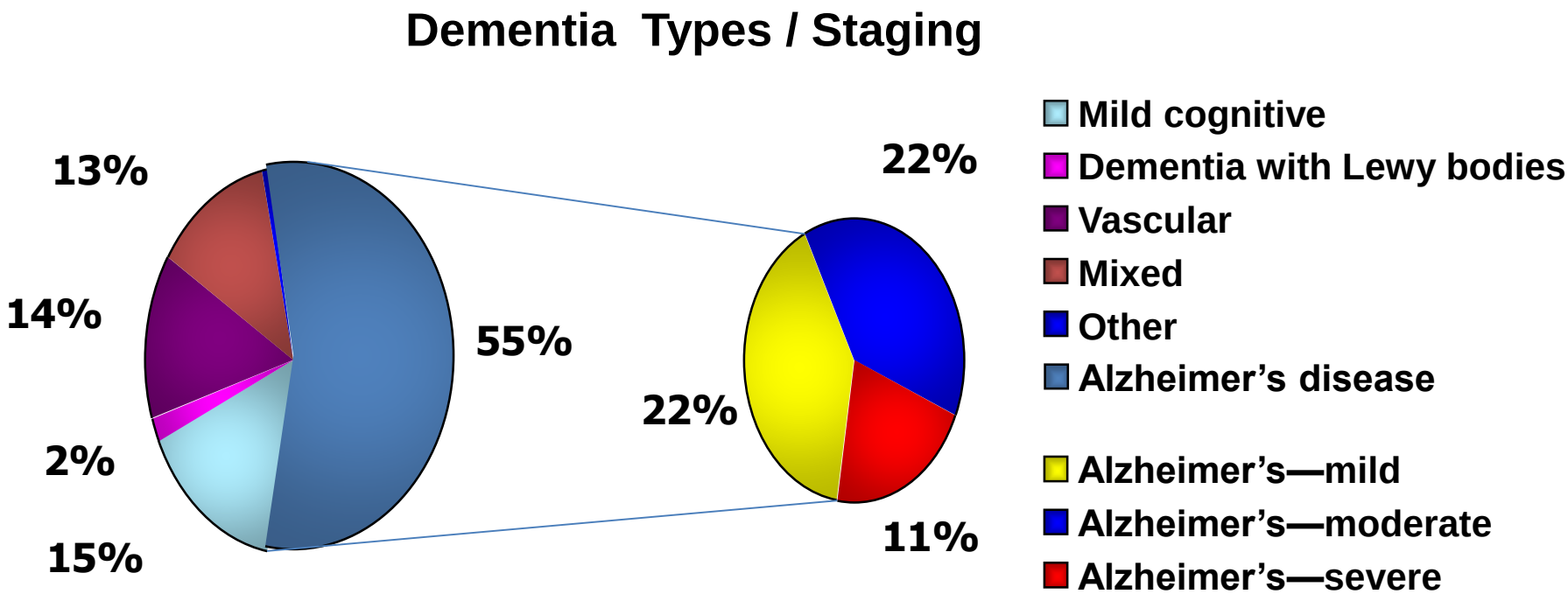
Alzheimer's Association website. 2017 Alzheimer's Disease Facts and Figures.

Typical Approach to Differential Diagnosis of Dementia



Break Down of Clinical Dementia Subtypes and Staging

About 2/5 of all patients are in each of the mild and moderate stages, and the remaining fifth are in the severe stage



What's the Difference When it Comes to Memory?

Alzheimer's Disease	Age-Related
▪ Poor judgment and decision making	▪ *Making a bad decision once in a while*
▪ *Inability to manage a budget*	▪ *Missing a monthly payment*
▪ *Losing track of the date or the season*	▪ *Forgetting which day it is and remembering later*
▪ *Difficulty having a conversation*	▪ *Sometimes forgetting which word to use*
▪ *Misplacing things and being unable to retrace steps to find them*	▪ *Losing things from time to time*

Alzheimer's Association

Dementia Syndromes: Vascular Dementia

- Should be reserved for patients with clear evidence of stroke on imaging or physical examination.
  - 10-40% of all dementia cases
  - 10-15% of AD cases are “mixed”- increasingly seen
  - Treatment focused on risk factors
    - smoking
    - atrial fibrillation
    - diabetes
    - hypertension

Frontotemporal Dementia

- Accounts for up to 3-20% of dementias
  - 4th behind AD and Lewy Body Dementia in neurodegenerative dementing illnesses

- Definition: clinicopathologic condition consisting of deterioration of personality and cognition assoc. with prominent frontal and temporal lobe atrophy

- Core features
  - Insidious onset and slow progression of domains affected in AD- hence often is not given appropriate medical attention
  - Early decline of
    - Social interpersonal conduct
    - Regulation of personal conduct
    - Insight
  - Early emotional blunting

Lewy Body Dementia

- Frequency: 15 – 20% of all dementias
  - Second most common dementia
- May be mixed with other dementias
  - Often misdiagnosed
- Shorter duration than AD: 6 – 10 years

Progressive cognitive decline with loss of normal social and occupational function: loss of memory, attention, frontal subcortical skills, visuospatial ability

Two of the following:

a. fluctuating cognition, attention, alertness

b. visual hallucinations

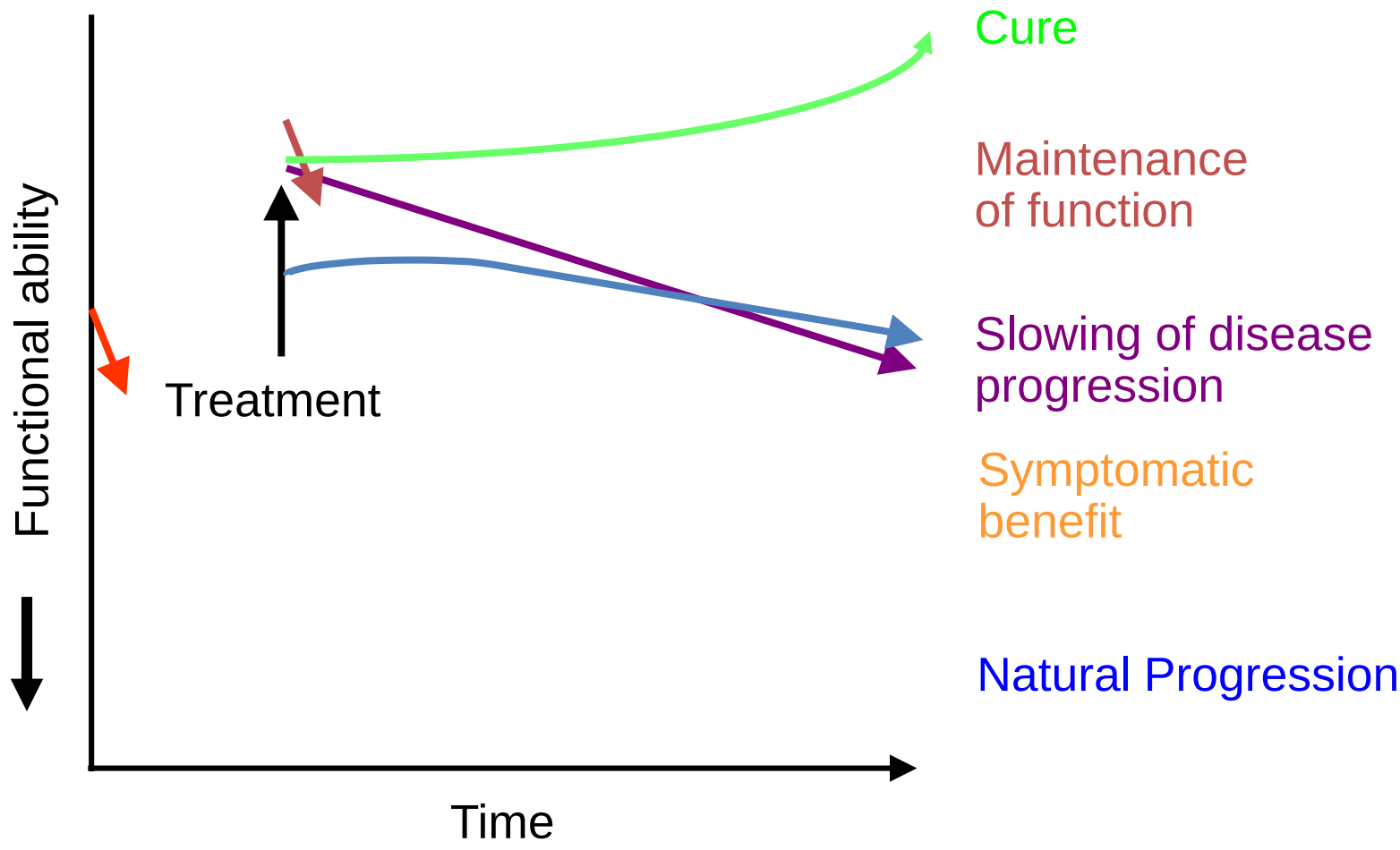
c. motor features of parkinsonism

Supportive features: falls, syncope, LOC, neuroleptic sensitivity, delusions, REM sleep disorders, Restless leg syndrome, Somnambulism—sleep walking

“Reversible” Causes of Dementia

- 10% of all patients with dementia; in reality, only 2-3% at most will truly have a reversible cause of dementia
- Medications
- Alcohol
- Metabolic (b12, thyroid, hyponatremia, hypercalcemia, hepatic and renal dysfunction)
- Depression? (likely marker though…)
- CNS neoplasms, chronic subdural

Treatment Outcomes in Alzheimer's Disease



Managing Alzheimer's Disease

- Optimize and *stabilize* physical, social, intellectual stimulation
- Maintenance of medical health
- Medication oversight/Monitor for delirium
- Maintain a Healthy diet
- Discuss possible changes in emotions and behavior that can occur, and how to mitigate them

- Review driving safety
- Discuss legal, financial issues
- Review relevant community resources
- Discuss coping strategies

- Discuss availability of clinical trials
- Establish ongoing monitoring plan

Treatments for Alzheimer's Dementia

Two types of treatments for cognitive symptoms

Cholinesterase inhibitors, e.g., Aricept

- Prolongs the activity of acetylcholine in the synapse.
- May work by improving vascularization
- Delay the worsening of mild cognitive impairment by 6-12 months

NMDA receptor antagonist

- Memantine
- Reduces glutamate excitotoxicity
- Temporarily delays worsening of moderate to severe cognitive impairment for some people

Pharmacologic Treatments for AD

MOA	Cholinesterase Inhibitors			NMDA-Receptor Antagonist
Drug	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**
Indication	Mild-moderate AD; severe AD	Mild-moderate AD	Mild-moderate AD	Moderate-severe AD
Initial dose	Tablet: 5 mg qd	Tablet/oral solution: 4 mg bid ER capsule: 8 mg qd	Capsule/oral solution: 1.5 mg bid Patch: 4.6 mg qd	Tablet/oral solution: 5 mg qd
Maximal dose	Tablet: 10 mg qd	Tablet/oral solution: 12 mg bid ER capsule: 24 mg qd	Capsule/oral solution: 6 mg bid Patch: 9.5 mg qd	Tablet/oral solution: 10 mg bid

ER = extended-release; MOA = mechanism of action; NMDA = *N*-methyl-D-aspartate.

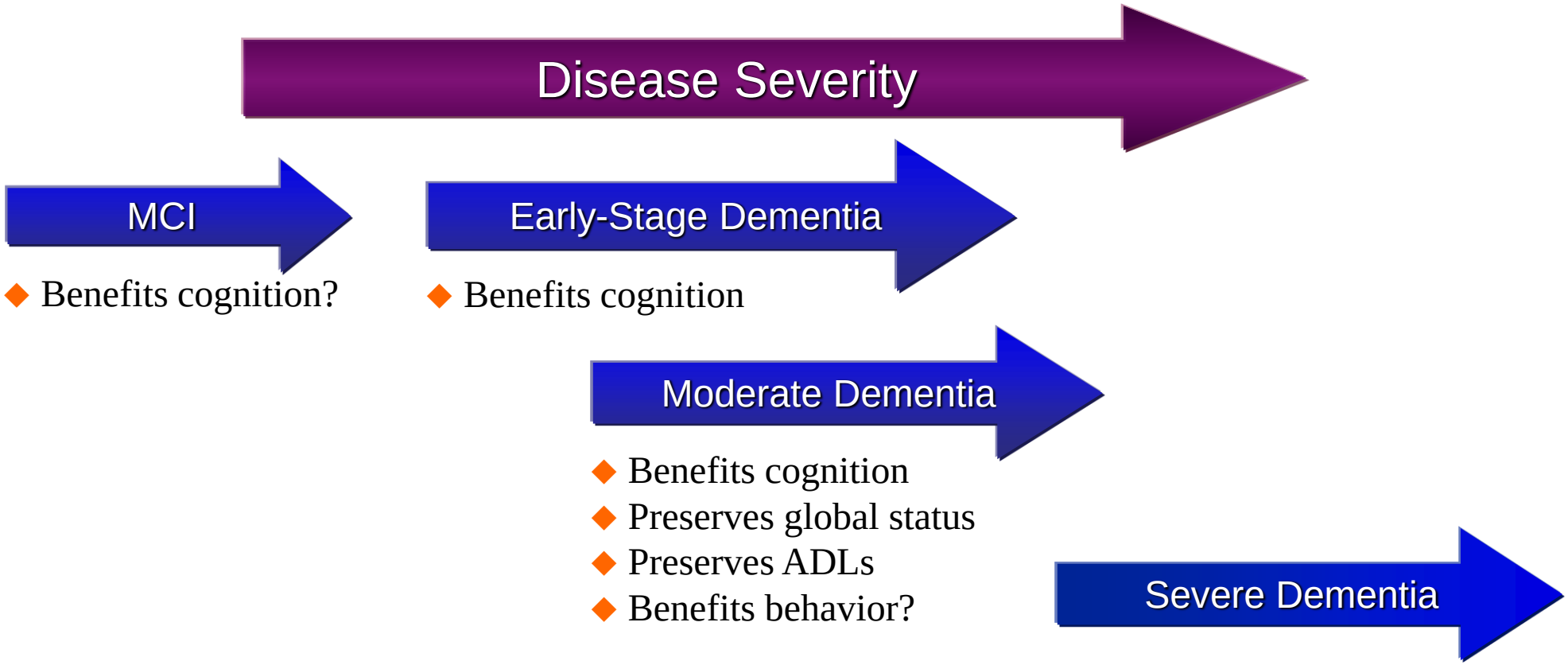
National Institute on Aging. Alzheimer's disease medications. November 2008. NIH Publication No. 08-3431. Available at: http://www.nia.nih.gov/Alzheimers/Publications/medicationsfs.htm.

Common Side Effects

Cholinesterase Inhibitors	NMDA-Receptor Antagonist
• Nausea/Vomiting • Diarrhea • Weight loss • Loss of appetite • Muscle weakness/cramping • Excessive dreaming	• Dizziness • Headache • Constipation • Confusion

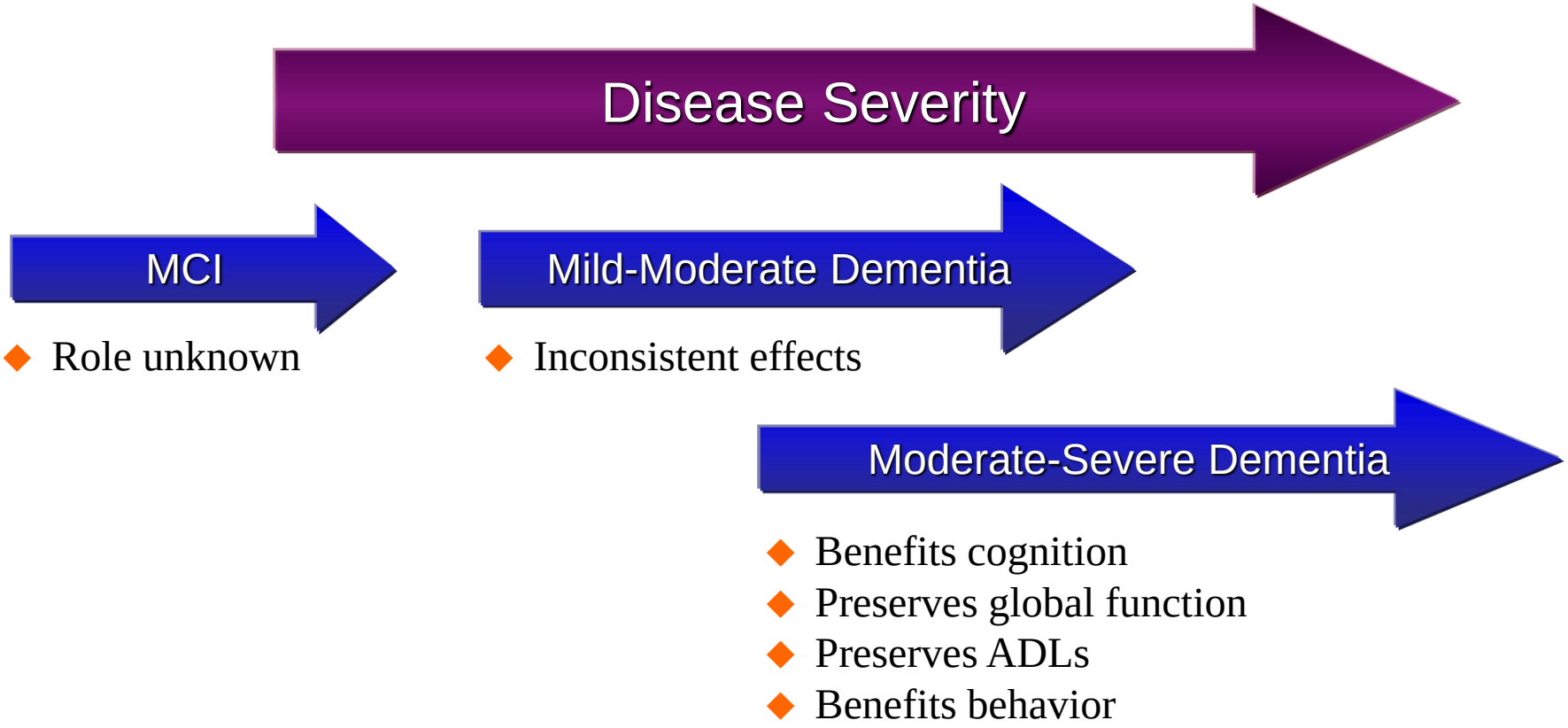
National Institute on Aging. Alzheimer's disease medications. November 2017. Available at https://www.nia.nih.gov/health/alzheimers-dementia-resources-for-professionals

Cholinesterase Inhibitor Therapy in AD



Class approved for mild-moderate AD
Donepezil also approved for severe AD

Memantine Therapy for AD*



*Approved in US for moderate-severe A, alone or in combination with cholinesterase inhibitors

Benefits of Early Alzheimer Diagnosis: Social

- Undiagnosed AD patients face avoidable problems
  - Social, financial
- Early education of caregivers
  - How to handle patient (choices, getting started)
- Advance planning while patient is competent
  - Will, proxy, power of attorney, advance directives
- Reduce family stress and misunderstanding
  - Caregiver burden, blame, denial
- Promote safety
  - Driving, compliance, cooking, etc.
- Patient's and family's right to know
  - Especially about genetic risks
- Promote advocacy
  - For research and treatment development

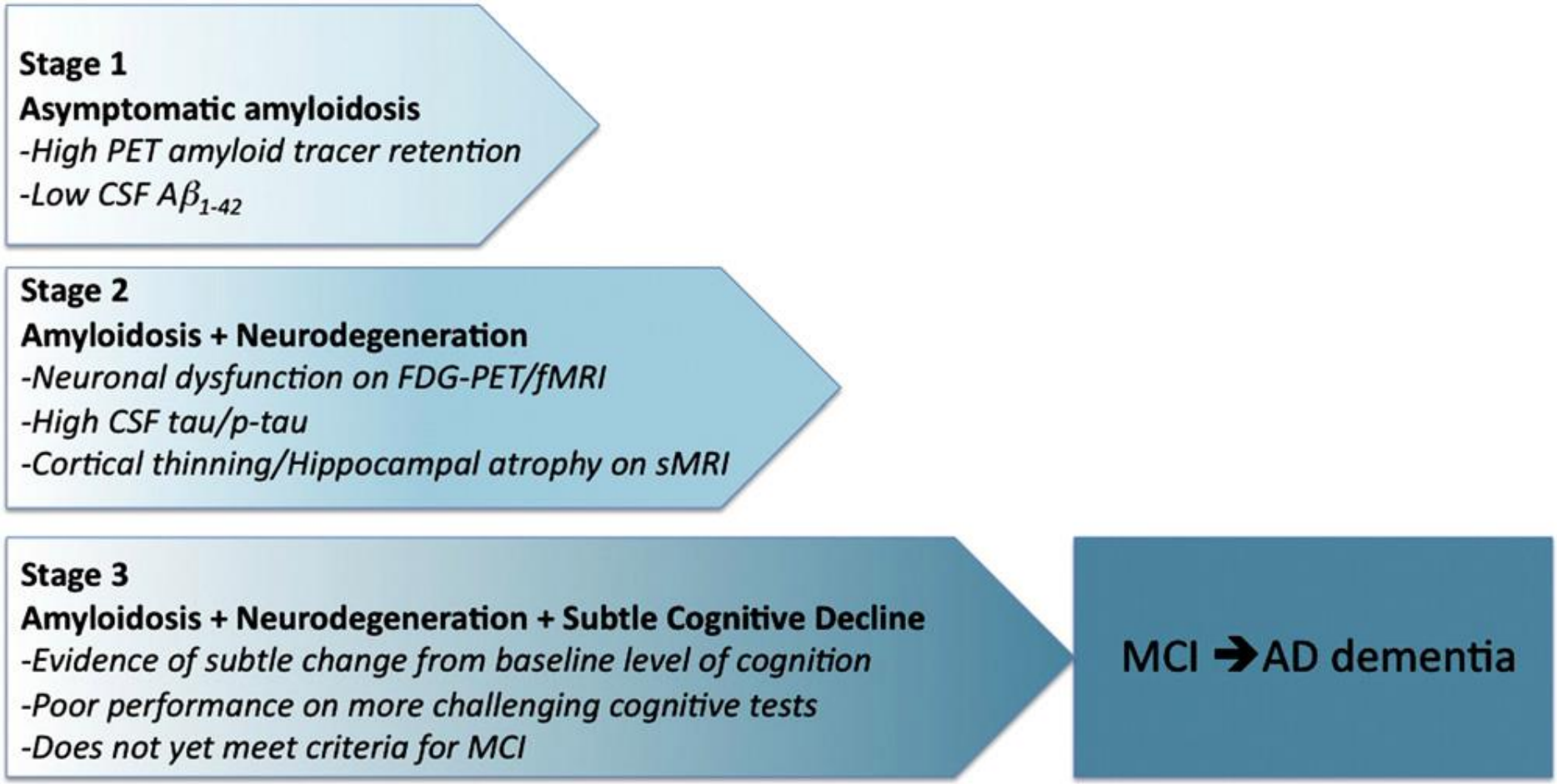
Diagnostic Criteria and Guidelines for Alzheimer's Disease

Four main goals:

- To better define the natural history of Alzheimer's disease from **asymptomatic stages** to full blown dementia
- To **relate the clinical symptoms**, as they emerge, to the underlying pathophysiology
- To use present knowledge to better diagnose the disease
- To define a **research agenda** that will help to extend our knowledge to better reach these goals

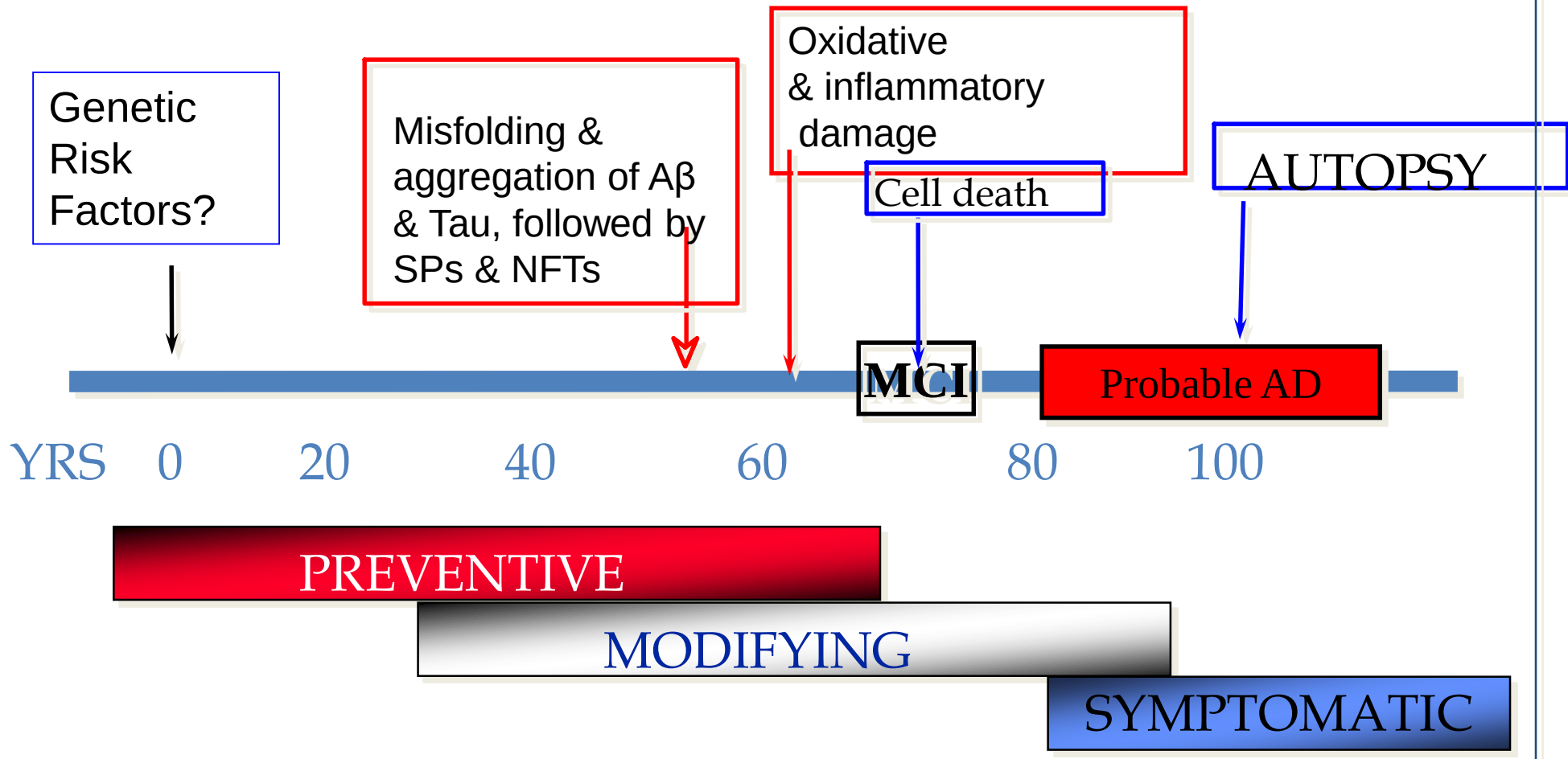
GM McKhann et al. http://dx.doi.org/10.1016/j.jalz.2011.03.005

Staging Framework for Preclinical AD



Sperling R et al *Alzheimer´s & Dementia* 2011

Pre Clinical to Alzheimer's Disease Timeline



Mild Cognitive Impairment

Cognitive impairment is disruptive to human well-being and psychosocial function

Cognitive Impairment is potentially a prodromal condition to dementia and Alzheimer's disease (AD)

Mild Cognitive Impairment- One impaired domain (amnestic or non amnestic)

Development of a Screening Plan

- **At age 50 years**: initial screen, review risks
  - Review dementia family history
  - Review of systems, vital signs
  - Brief cognitive evaluation – establish baseline for longitudinal assessment -MoCA
  - Complete blood count (CBC), B_{12}, cholesterol
  - Begin yearly assessments if high risk
- **At age 55–60 years**: follow-up assessments
  - Review of systems, vital signs
  - Brief cognitive evaluation using longitudinal measures- MoCA
  - CBC, B_{12}, cholesterol
- **At age 65 years** and older: begin **annual assessments**
  - Review of systems, vital signs
  - Brief cognitive evaluation watching longitudinal changes
  - CBC, B_{12}, cholesterol

Development of a In-depth Screen:

- More cognitive testing- Can send out for Neuropsychological Testing
  - Test ability to name animals and vegetables in 1 minute
  - Ask for recall of 10 items after distraction
  - Test praxis
  - Draw clock, cube
  - Logical Memory Story Test

- Talk with a knowledgeable informant
- Ask questions about activities of daily living
- Ask questions about depression, sleep

Cognitive Assessments

- Brief objective measures:
  - Mini-Cog
  - Mini-Mental State Exam (MMSE)
  - Montreal Cognitive Assessment (MOCA)
- Free online, public domain (except MMSE)
- Can have an assistant/MA administer these tests

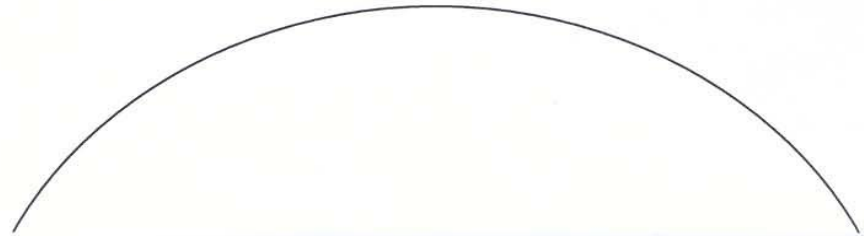
Mini-Cog

CLOCK DRAW TEST

Patient name_____
Patient ID #_____
Date__/__/__

1) Inside the circle, please draw the hours of a clock as they normally appear

2) Place the hands of the clock to represent the time: “ten minutes after eleven o’clock”



MMSE

MMSE®

Date of Examination ___/___/___ Examiner _____

Name _____ Age _____ Years of School Completed _____

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? **May I ask you some questions about your memory?**

ORIENTATION TO TIME		RESPONSE	SCORE (circle one)	
What is the...	**year?**		0	1
	season?		0	1
	month of the year?		0	1
	day of the week?		0	1
	date?		0	1

ORIENTATION TO PLACE*				
Where are we now? What is the...				
	state (province)**?**		0	1
	county (or city/town)**?**		0	1
	city/town (or part of city/neighborhood)**?**		0	1
	building (name or type)**?**		0	1
	floor of the building (room number or address)**?**		0	1

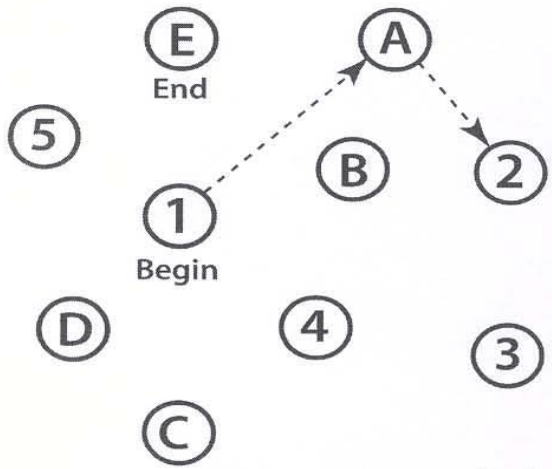
*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

MOCA

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



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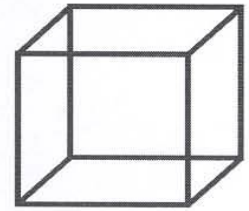


Copy cube

[ ]

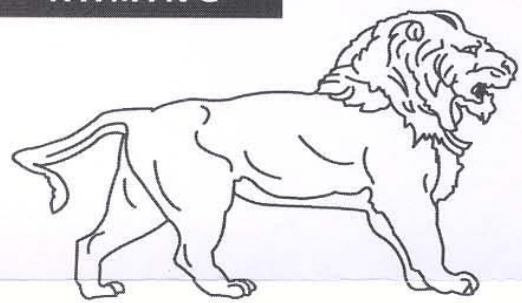
Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS

___/5

NAMING



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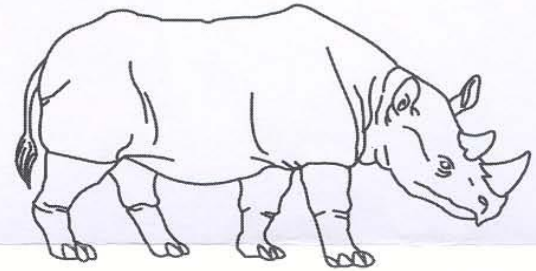

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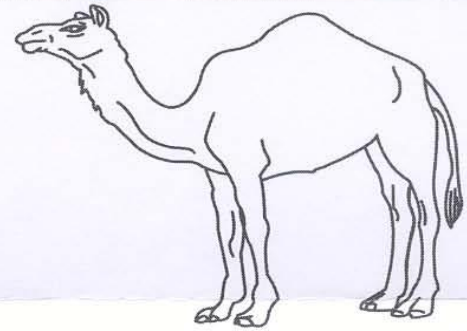

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Factors associated with cognitive decline and risk of Alzheimer's disease

Risk Factors

- **Age**
- **Women**
- Genetic mutations
  - Apolipoprotein E ε4 allele *
- Diabetes*
- **Cardiovascular/ Cerebrovascular disease***
- Depressive symptoms*
- Psychological distress
- Parkinsonian signs
- Race/Ethnicity
- *effect stronger in women

Protective Factors

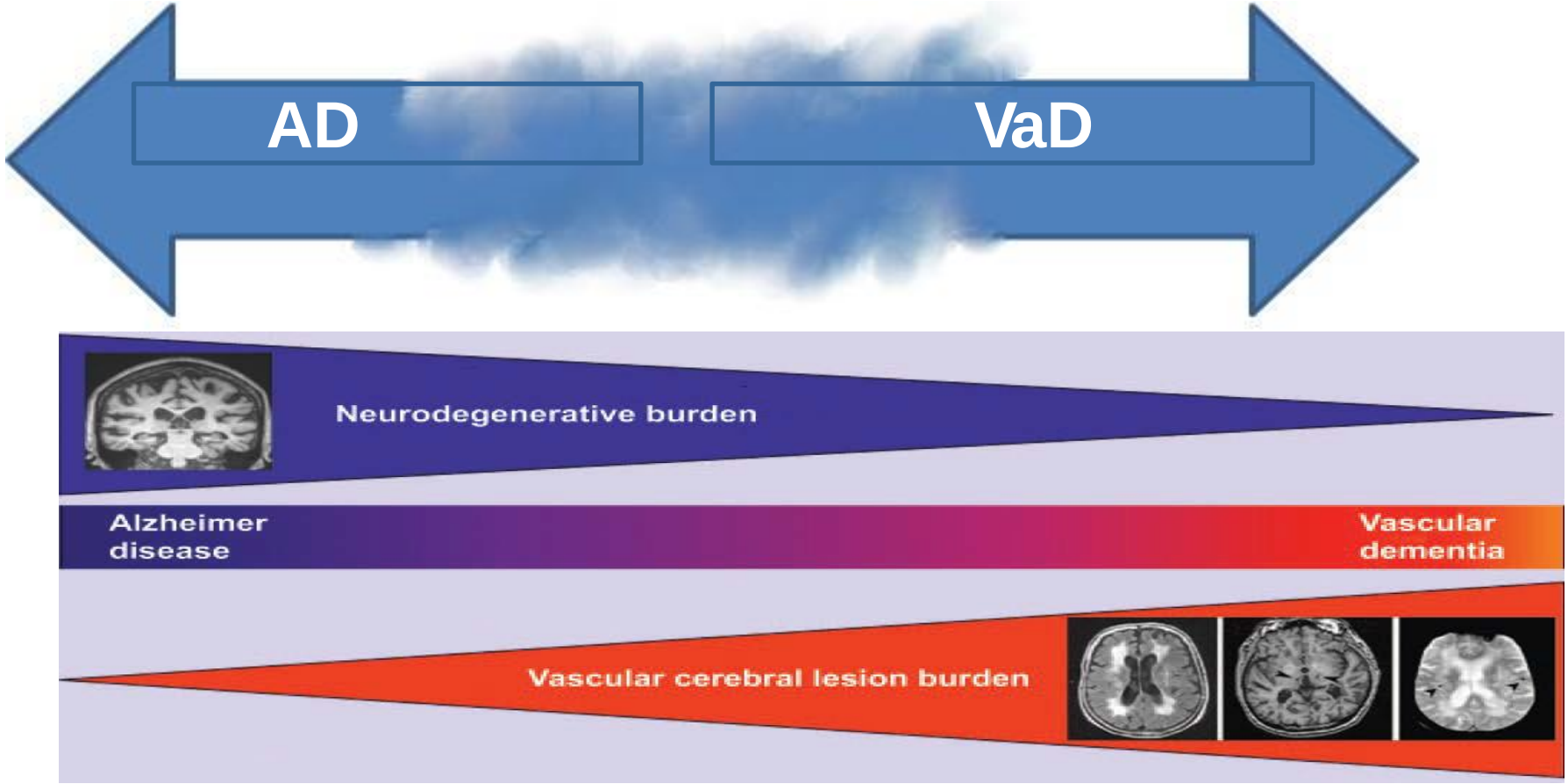
- Apolipoprotein E ε2 allele
- Years of education
- Cognitive activities
- Physical activities *
- Social activities
- Estrogen- timing

Other Risk Factors – with noted Sex Differences

- Head injury- **rates of concussion may be higher in women leading to increased head injuries and AD**
- Low serum levels of folate and vitamin B12- **due to social isolation and living alone, increased in women**
- Elevated plasma and total homocysteine levels-**elevated in women with Alzheimer's disease**
- Fewer years of formal education- **stronger effect in women**
- Lower income -lower occupational status- **stronger effect in women**
- Hormonal **status-decline in estrogen- Increased risk of AD for women***


HEART BRAIN

Dementia in advanced age



Both vascular and degenerative mechanisms often contribute to dementia development in older adults

Viswanathan, et al., Neurology 2009

Diabetes – A Strong Risk Factor for Cognitive Dysfunction and Alzheimer's disease (AD)

- Type I and Type II diabetes can → heart disease, stroke, renal failure, cognitive dysfunction and AD
- Duration of diabetes esp. important risk factor for AD
- Hyperinsulinemia and hyperglycemia preceding overt diabetes, also increase risk of cognitive changes and AD
- Metabolic changes associated with diabetes such as: oxidative stress, alteration in glucose and fatty acid metabolism, inflammation, accumulation of oxidatively altered and glycated proteins, are also associated with AD

STATINS AND COGNITION

14 randomised placebo-controlled trials (28,621 pts), 9 observational studies (various designs 319,636 pts), 1 case series and 5 case reports were included.

- 11 trials investigated the effect of statins compared with placebo on cognition as a primary endpoint.
- 1 trial found that simvastatin had a negative impact on cognitive effects in tests that had previously been shown to be statin-sensitive.
- 1 trial reported significant cognitive improvements in a number of cognitive measures with placebo but only an improvement in memory recall with lovastatin.
- 2 trials reported significant improvements in cognition with lovastatin, pravastatin and atorvastatin.
- 7 trials did not report any significant differences between statins and placebo on measures of cognition.
- 3 trials measured cognition as a secondary endpoint: one reported an improvement in verbal memory with atorvastatin but no effect on cognitive function
- 2 reported no significant differences in cognitive decline between pravastatin or simvastatin and placebo.

•4 of 9 observational studies reported possible protective or beneficial effects of statins, three reported no effects of statins on cognition and one study reported an increased risk of delirium.

•The case reports included people who took simvastatin, atorvastatin and rosuvastatin and

No consistent studies, may be beneficial for cognitive function in some patients.

Rojas-Fernandez CH1, Cameron JC. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. Ann Pharmacother. 2012 Apr;46(4):549-57. doi: 10.1345/aph.1Q620. Epub 2012 Apr 3.

The NEW ENGLAND JOURNAL of MEDICINE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

- At 1 year, the mean SBP was 121.4 mm Hg in the intensive treatment group and 136.2 mm Hg in the standard-treatment group.
- The intervention was stopped early after a median follow-up of 3.26 years - significantly lower rate of the primary composite outcome* in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; (P<0.001)
- All-cause mortality was also significantly lower in the intensive treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003).
- Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive treatment group than in the standard-treatment group.

- *The primary composite outcome: myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.
- With permission: Alan Lerner, MD

SPRINT-MIND Hypotheses

Over an 60 months, the incidence of all-cause dementia and mild cognitive impairment will be lower in SPRINT participants assigned to the intensive SBP treatment arm compared to the standard SBP treatment arm

1) The increase in WML volume will be lower in participants randomized to an intensive systolic BP treatment goal of <120 mmHg compared to their counterparts randomized to a standard systolic BP treatment goal of <140 mmHg.
2) Declines in total brain volume will be lower in the intensive treatment group, reflective of less atrophy.

Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment

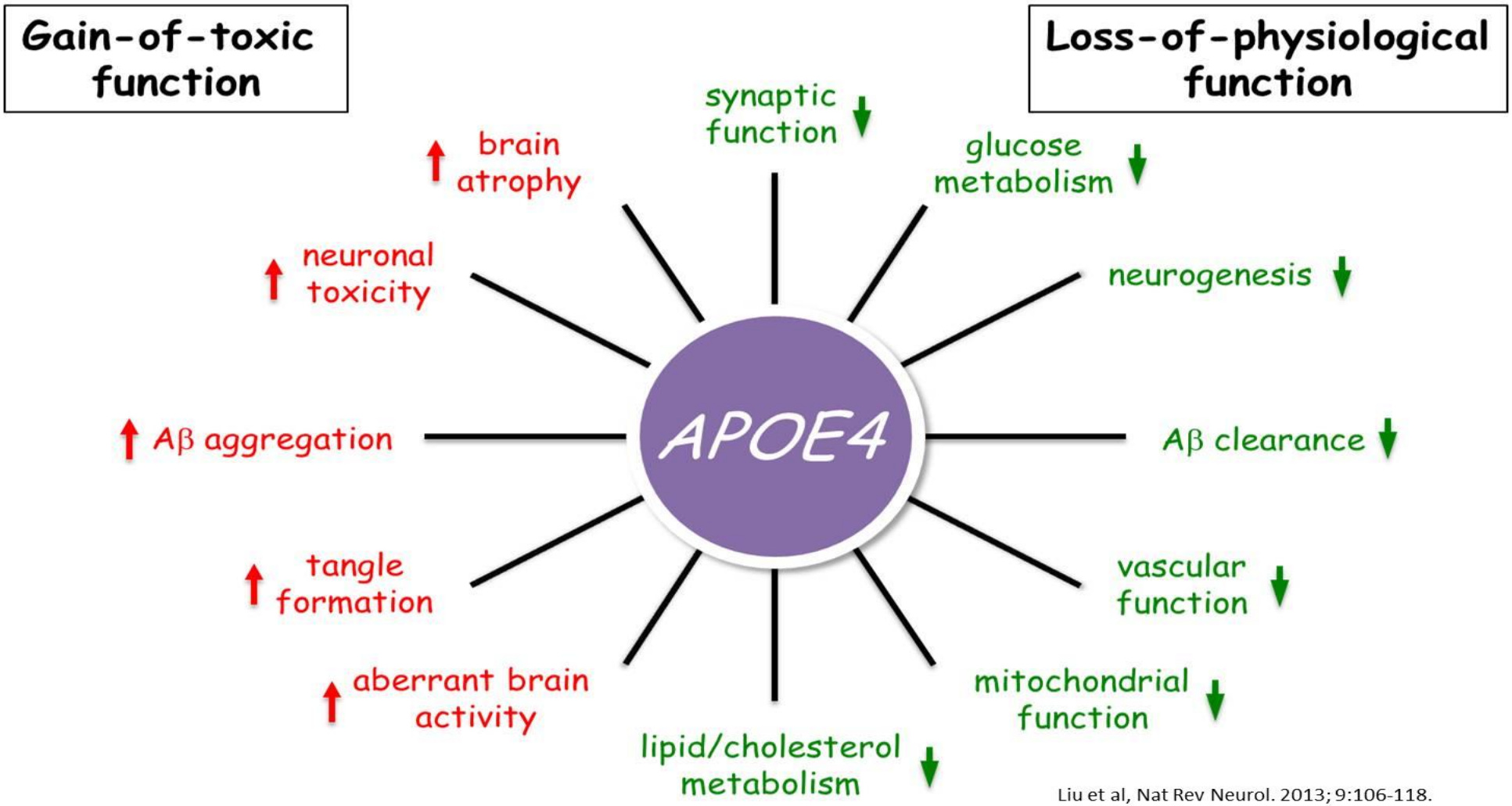
Group	Intensive Treatment		Standard Treatment			
Outcome	No. of Patients / Total (%)	% per year	No. of Patients / Total (%)	% per year	Hazard Ratio (95% CI)[a]	P value
Probable Dementia	147 / 4,278 (3.4)	0.72	175 / 4,284 (4.1)	0.86	0.83 (0.67 - 1.04)	0.10
Mild Cognitive Impairment	**285 / 4,201 (6.8)**	**1.45**	**348 / 4,209 (8.3)**	**1.81**	**0.81 (0.70 - 0.95)**	**0.01**
Composite of Mild Cognitive Impairment or Probable Dementia	**398 / 4,278 (9.3)**	**2.01**	**463 / 4,284 (10.8)**	**2.38**	**0.85 (0.74 - 0.97)**	**0.02**

Genetics of Alzheimer's Disease

- AD is genetically heterogeneous:
  - 25% is familial (i.e., two or more in a family are affected).
    - Of these:
      - 95% is late-onset (after age 65 years) – APOE 4
      - 5% is early-onset (before age 65 years) – Presenilin 1 and 2
  - 75% is sporadic

- Genetic counseling of persons with AD and family members

- First-degree relatives of a person with AD have a cumulative lifetime risk of developing AD of about 15–30%, this risk is about 2.5 times that of the background risk (27% vs. 10.4%).



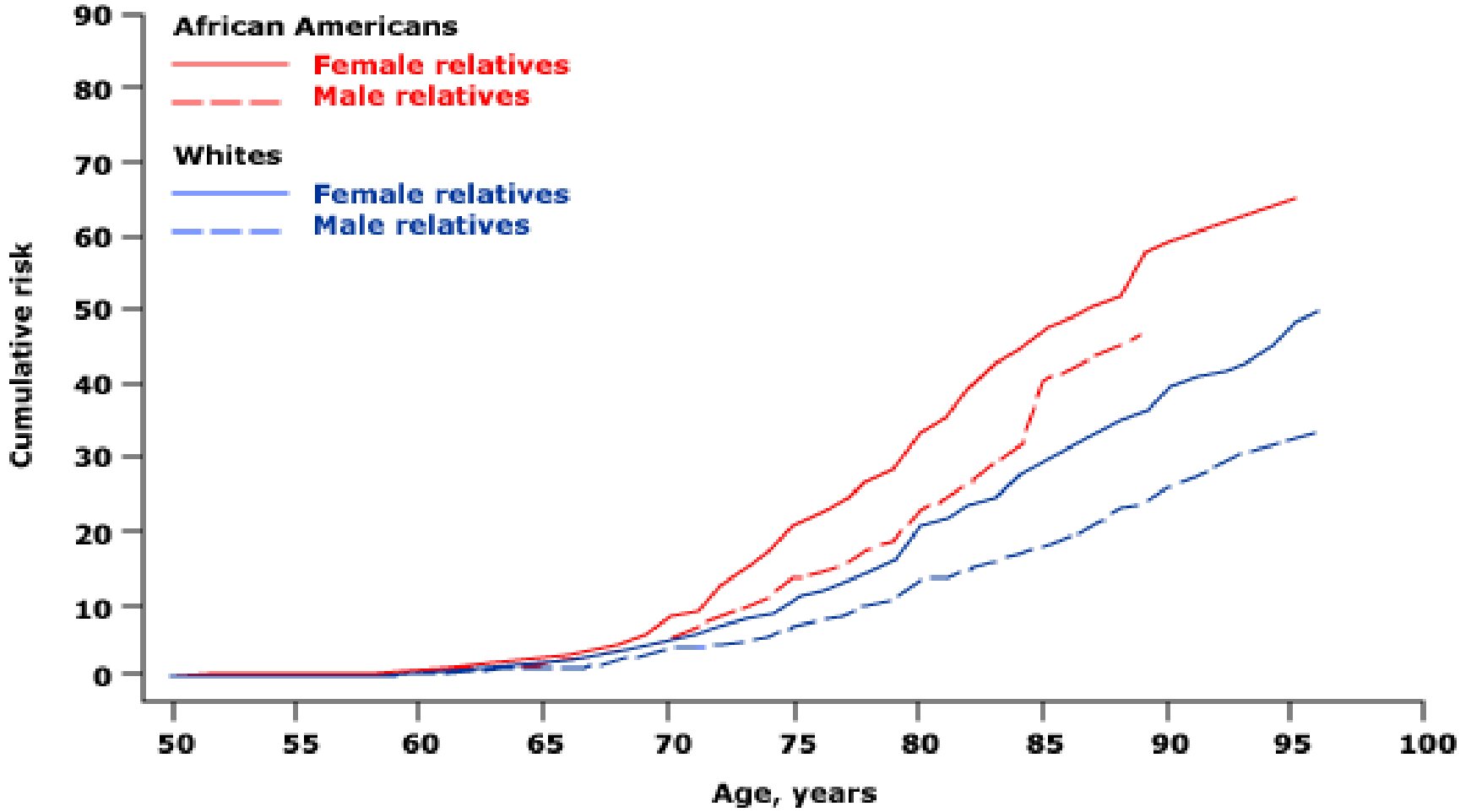
Liu et al, Nat Rev Neurol. 2013; 9:106-118.

ApoE in Centenarians

- More likely to have ApoE2 (12.8% vs. 6.8% in controls)
- Less likely to have ApoE4 (5.2% vs. 11.2% in controls)
- Equally likely to have ApoE3 (82% for both)

Schaechter F et al. Nature Genetics 1994

Family History



Green RC, et al. JAMA 2002

Sleep and Amyloid plaques

Sleep deprivation caused elevated Aβ in interstitial fluid (ISF) in the brains of normal mice

Aβ levels decreased as soon as they fell asleep

Neuropeptide orexin causes wakefulness and increased Aβ in the ISF

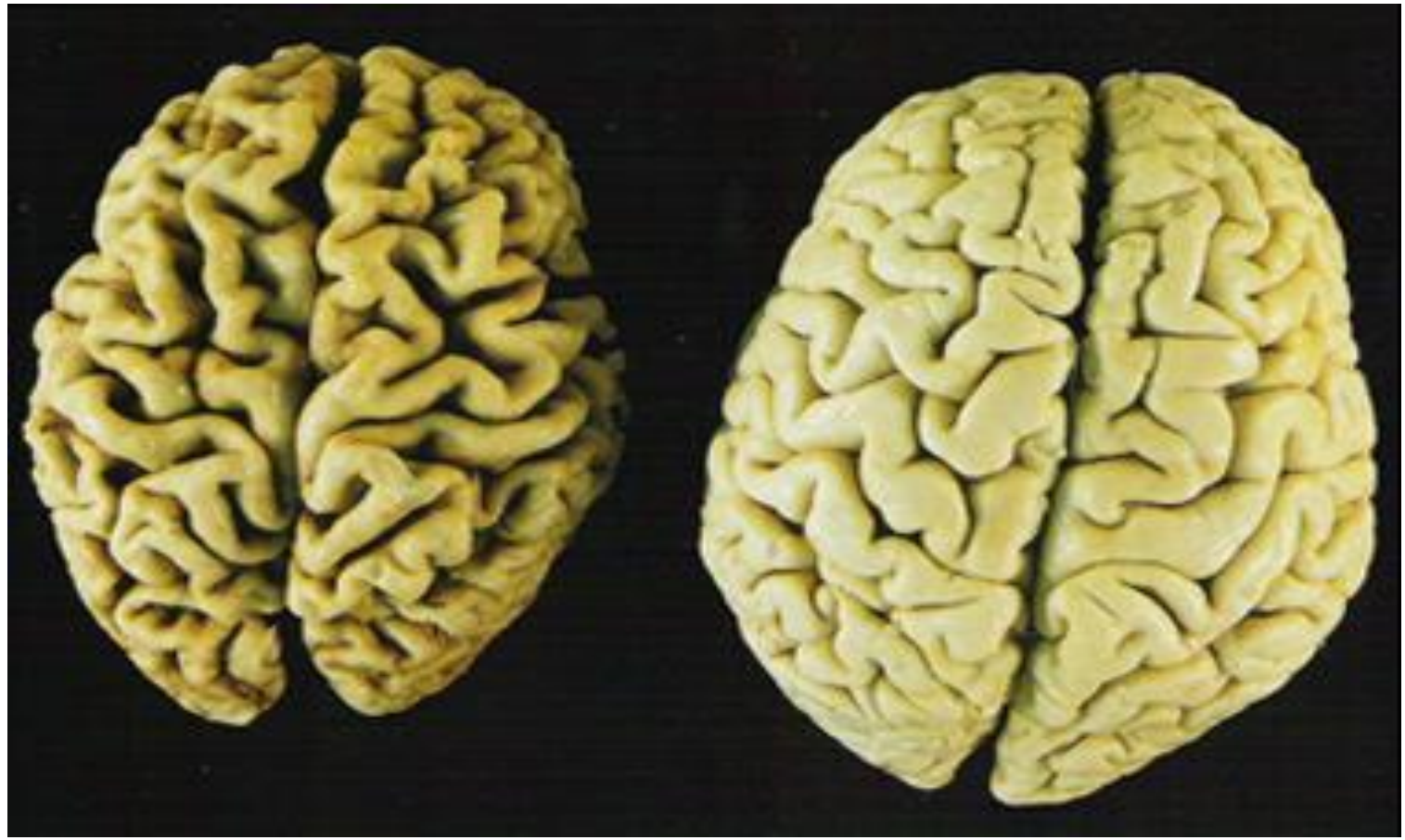
Sleep deprivation of transgenic Alzheimer's mice
- Increased Aβ plaque deposition
- Orexin receptor antagonist decreased plaque formation

Sleep disturbances are common in people with neurodegenerative disorders.

Kang, J-E. et al., *Science* 9/24/09, From *Nature Reviews of Neuroscience* 10/14/09.


Dang!.. Now where was I going?

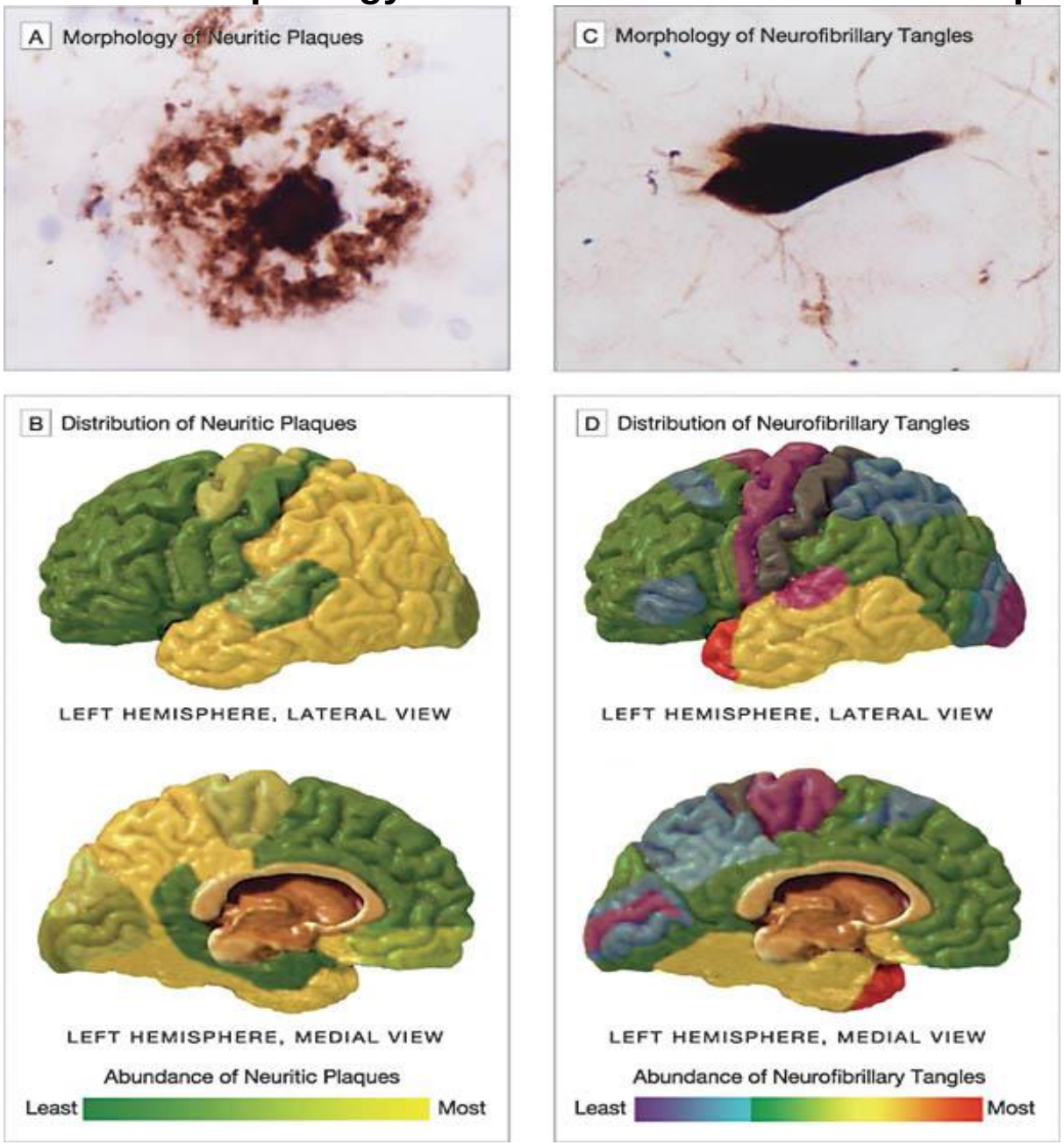
Brain Atrophy in Alzheimer's disease



Alzheimer's Disease

Normal

Morphology and Distribution of Neuritic Plaques and Neurofibrillary Tangles



Pathologic diagnosis of AD require the presence of both neuritic plaques and neurofibrillary tangles in excess of the abundance anticipated for age-matched healthy controls.

Neuritic plaques consist of a central core of amyloid protein.

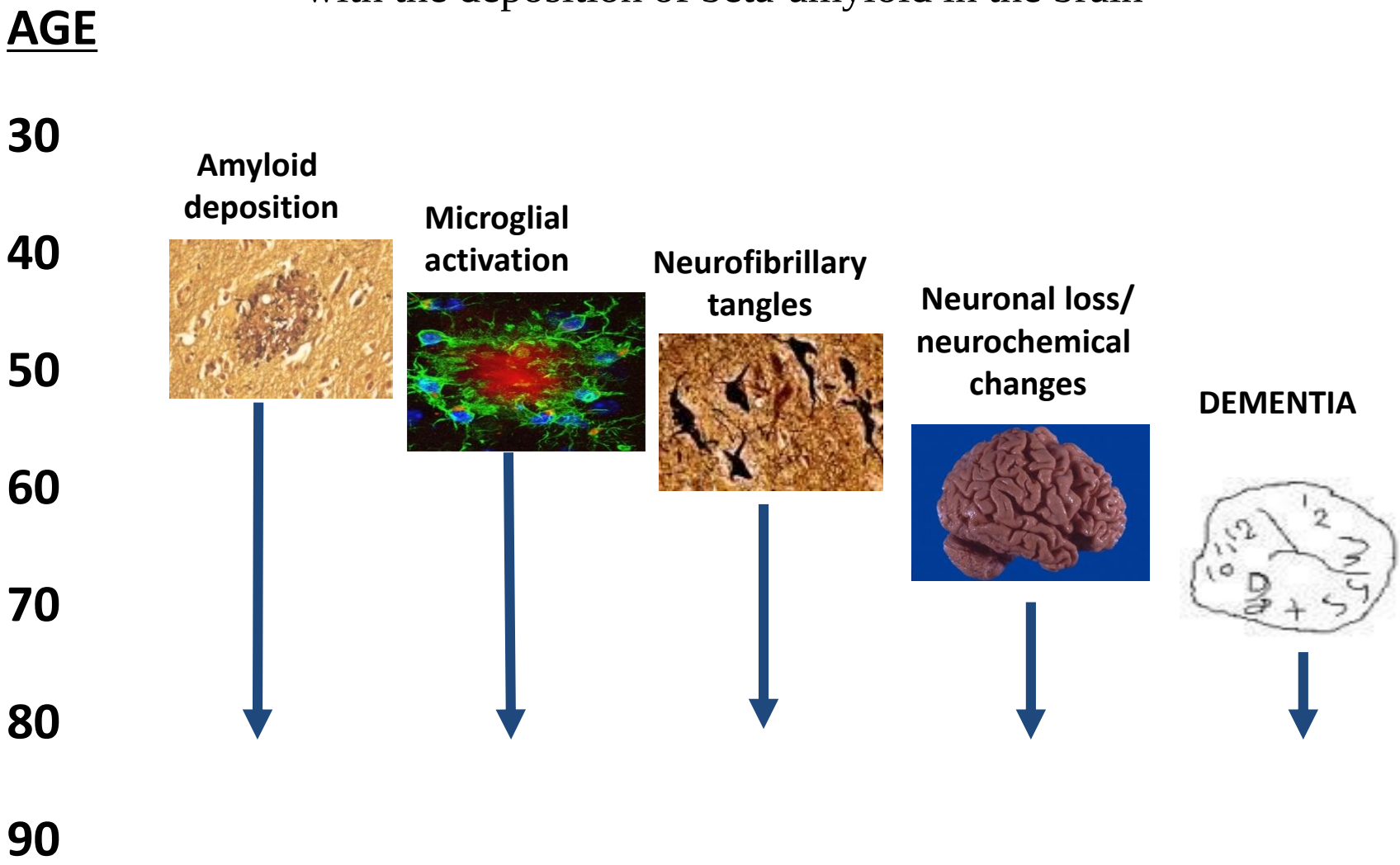
Neurofibrillary tangles are the second major feature of AD. They contain paired helical filaments of abnormally phosphorylated tau protein that occupy the cell body and extend into the dendrites

Cummings JL. et al. JAMA 2002

JAMA

The Original Amyloid Cascade Hypothesis

Alzheimer's is the cumulative product of a series of pathological events that may begin with the deposition of beta-amyloid in the brain



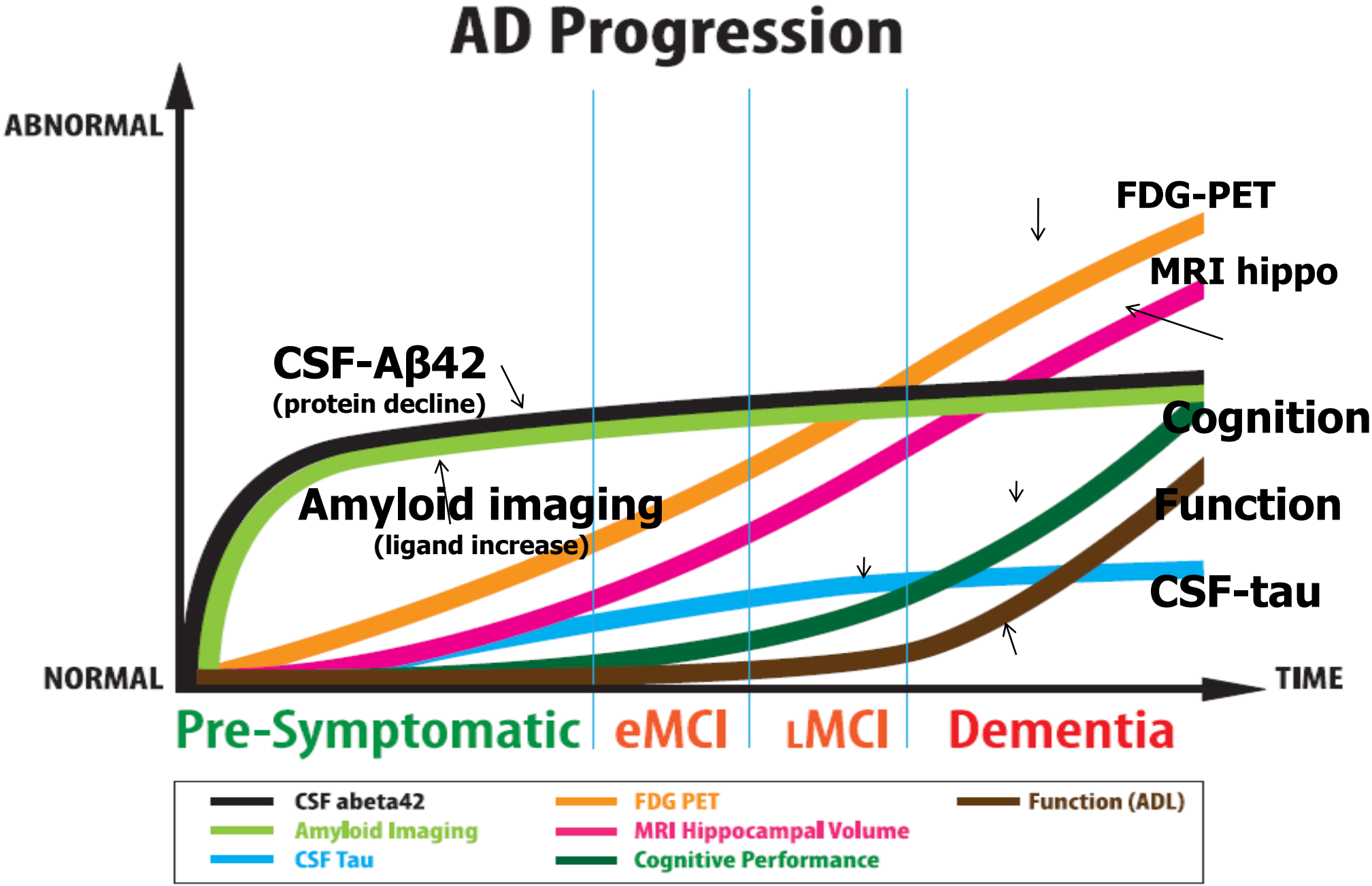
Potential Therapies for AD

1. **Reduce Aβ production**
    1. Inhibit beta-secretase
    2. Inhibit gamma-secretase
    3. Enhance alpha-secretase
2. **Increase Aβ clearance**
    1. Increase LRP1, decrease RAGE
    2. Immunomodulators
    3. Vaccinate against Aβ
3. **Reduce Aβ toxicity**
    1. Beta breakers
    2. Metal chelators
    3. Anti-oxidants, e.g., Vitamin E
    4. Block ApoE4- Aβ interaction
4. **Repair Aβ damage**
    1. Gene therapy, e.g., expression of BDNF, NGF
5. **Tau tangle targets**, e.g., kinase inhibitors

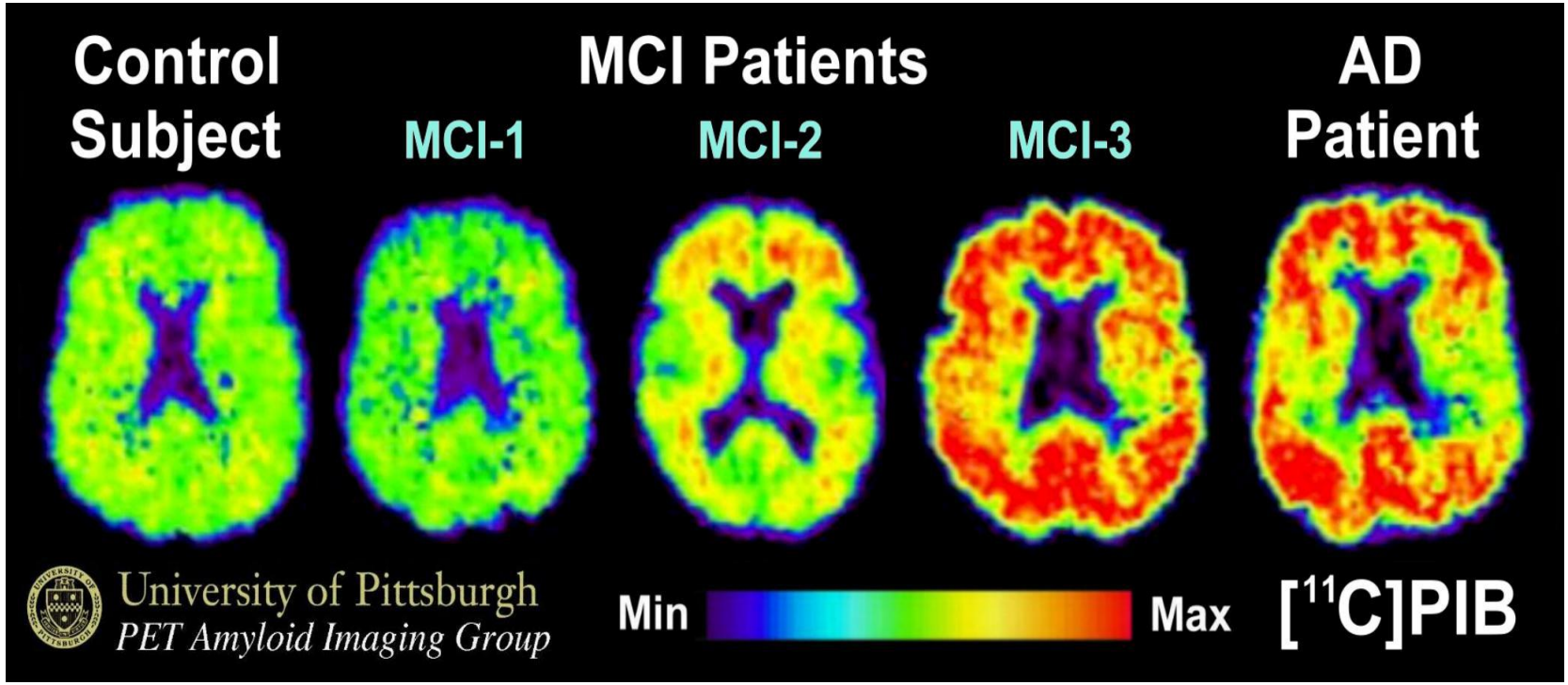
Recent AD Phase 3 Candidate Therapies

Compound	Target	Type	MOA
Aducanumab	Aβ	Fully human IgG1 mAb	Passive immunotherapy
Crenezumab	Aβ	Humanized mAb	Passive immunotherapy
Gantenerumab	Aβ	Fully human mAb	Passive immunotherapy
Solanezumab	Aβ	Humanized mAb	Passive immunotherapy
ALZT-OP1	Aβ	Small Molecule	Anti-inflammatory
AZD3293	Aβ	Small molecule	BACE inhibitor
CNP520	Aβ	Small molecule	BACE inhibitor
Elenbecestat	Aβ	Small molecule	BACE inhibitor
Verubecestat	Aβ	Small molecule	BACE inhibitor
AGB101	Aβ	Small molecule	Anti-epileptic drug
Azeliragon	Aβ	Small molecule	RAGE inhibitor
RVT-101	Other	Small molecule	$5HT_6$ receptor antagonist
LMTM and LMTX	Tau	Small molecule	Tau aggregation inhibitor

Alzforum website. Therapeutics database.


AD Progression
ABNORMAL
NORMAL
TIME
FDG-PET
MRI hippo
CSF-Aβ42
(protein decline)
Cognition
Amyloid imaging
(ligand increase)
Function
CSF-tau
Pre-Symptomatic
eMCI
LMCI
Dementia
CSF abeta42
Amyloid Imaging
CSF Tau
FDG PET
MRI Hippocampal Volume
Cognitive Performance
Function (ADL)

Individuals with MCI Cover the Range of Amyloid Load



PET images obtained with the amyloid-imaging agent, Pittsburgh Compound-B ([^{11}C]PIB) in a normal control (far left), three different patients with mild cognitive impairment (MCI; center images) and a mild AD patient (far right). Some MCI patients have control-like levels of amyloid, some have AD-like levels of amyloid and some have intermediate levels.

Population Platforms for Clinical Trials

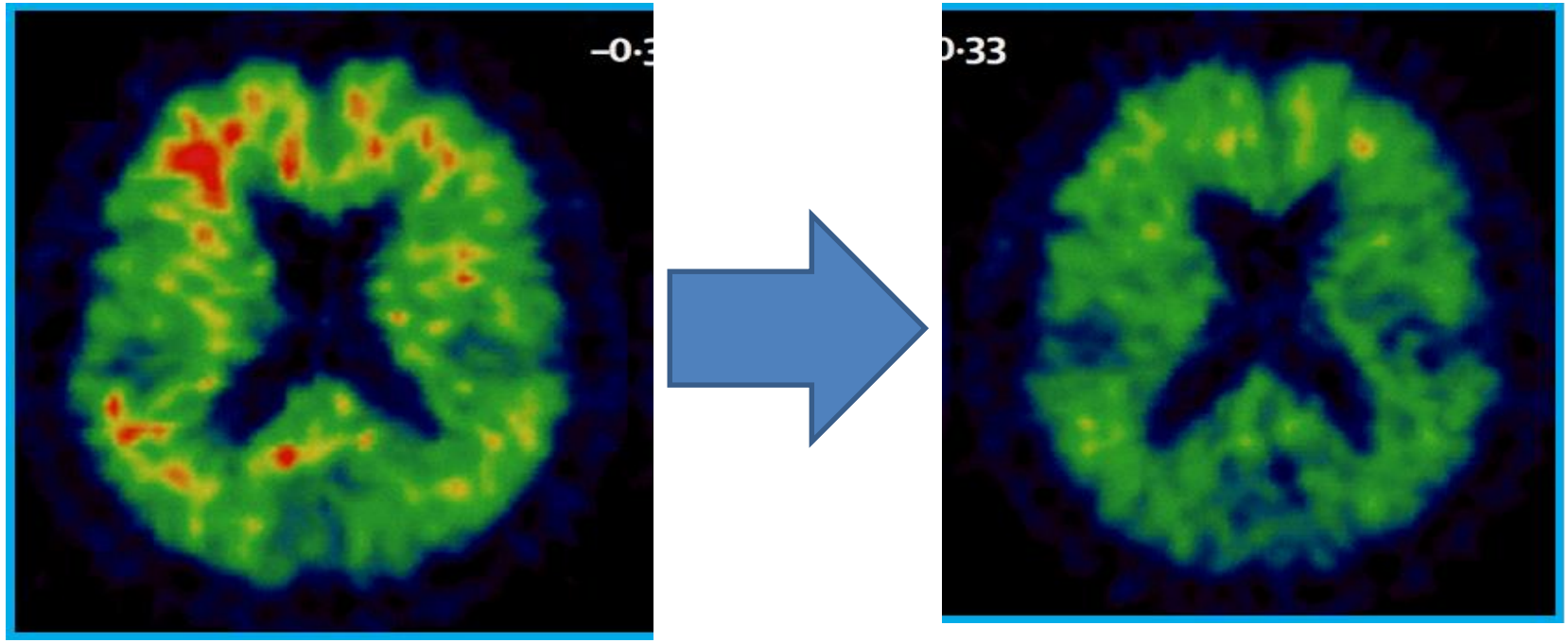
A4 Study

Generation Study

Lifestyle Studies – Diet and Exercise

A4 Trial: Anti-Amyloid in Asymptomatic Alzheimer's

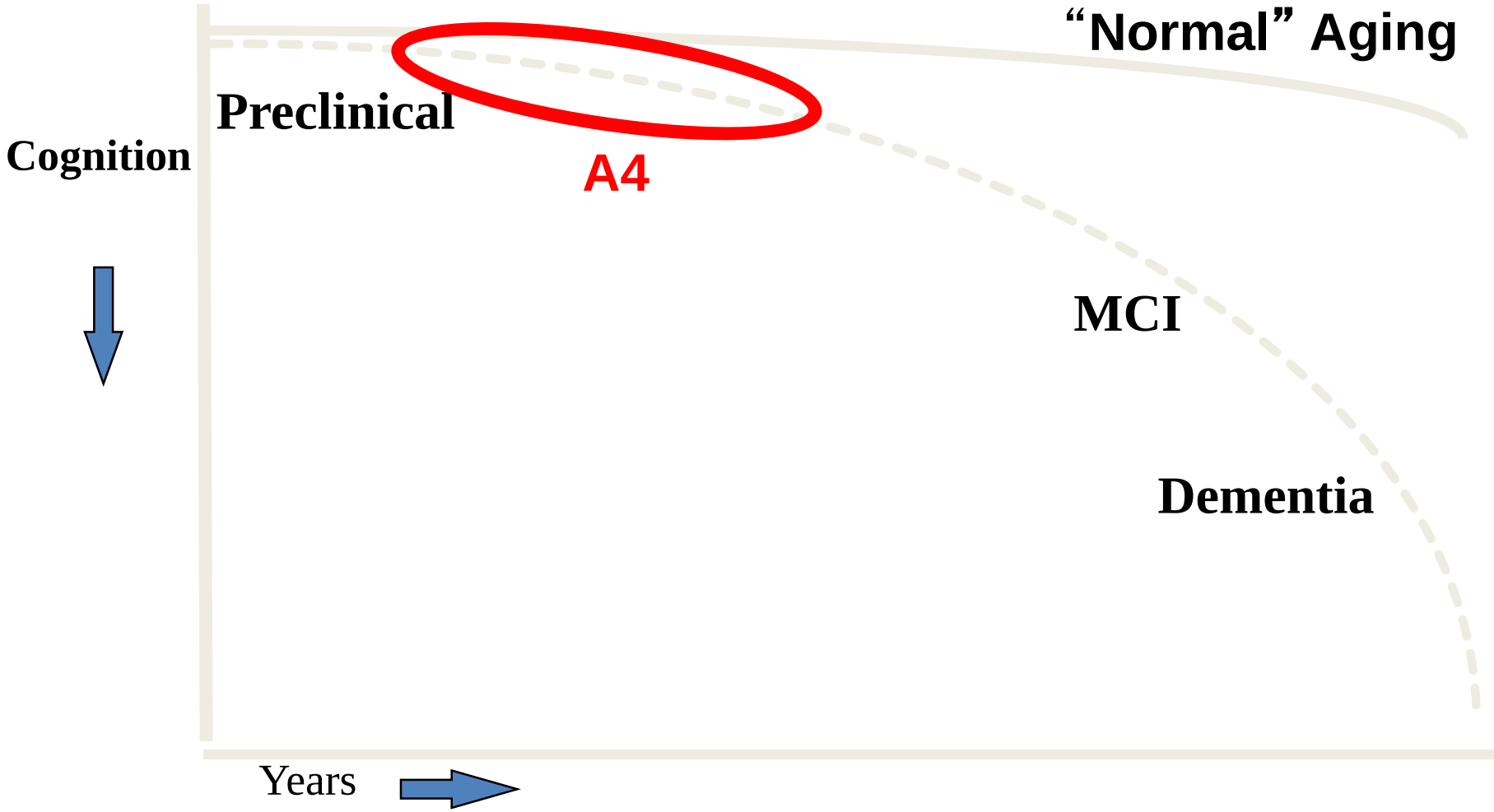
- Screened over 10,000 adults 65-85 years of age
- 1,000 normal adults with positive Amyloid-PET
- What we hope to accomplish…



A4: The time is now

http://a4study.org/

Continuum of Alzheimer's Disease



Adapted from Sperling et al *Alz & Dementia* 2011

GENERATION Studies 1 and 2

- Generation 1: Assess two anti amyloid drugs in cognitively normal persons, 60-75 yrs at risk for the onset of clinical symptoms of Alzheimer's disease (AD) **APOE4/E4** carriers

- Generation 2: A double-blind, placebo-controlled, adaptive design in cognitively normal persons aged 60 to 75 years, with at least **one APOE4** allele (Homozygotes or Heterozygotes) and, if Heterozygotes, with evidence of elevated brain amyloid on PET.

  - Primary Outcome Measures: Time to diagnosis of MCI due to Alzheimer's Disease (AD) or dementia due to Alzheimer's Disease

ALZHEIMER'S PREVENTION INITIATIVE

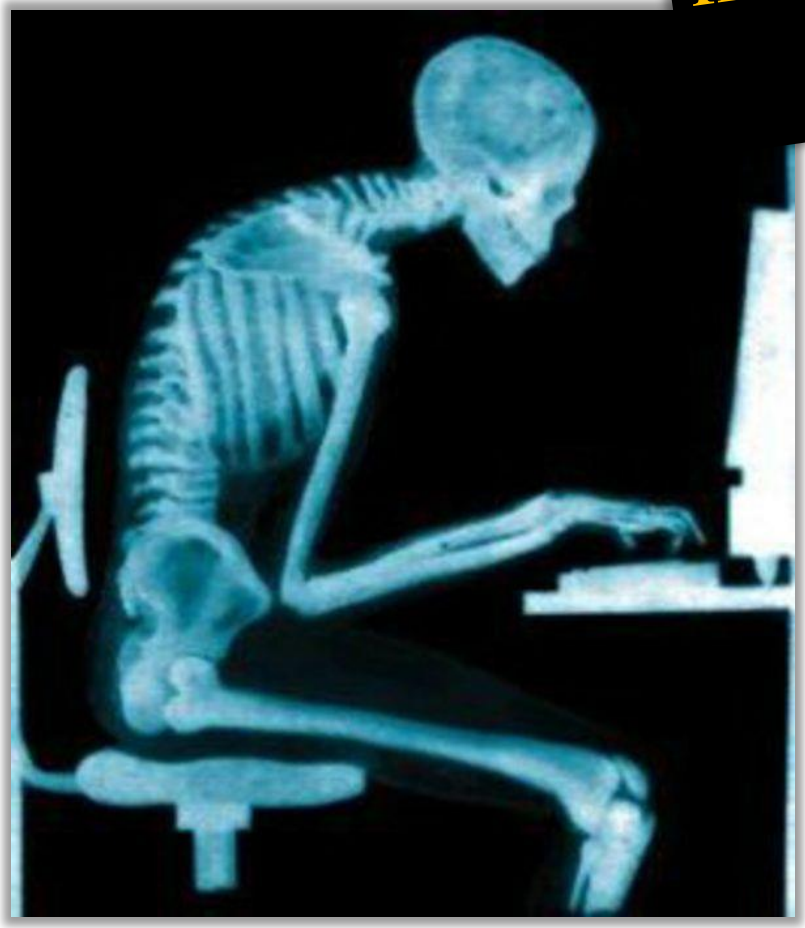
https://www.generationprogram.com/

ALZHEIMER'S PREVENTION INITIATIVE

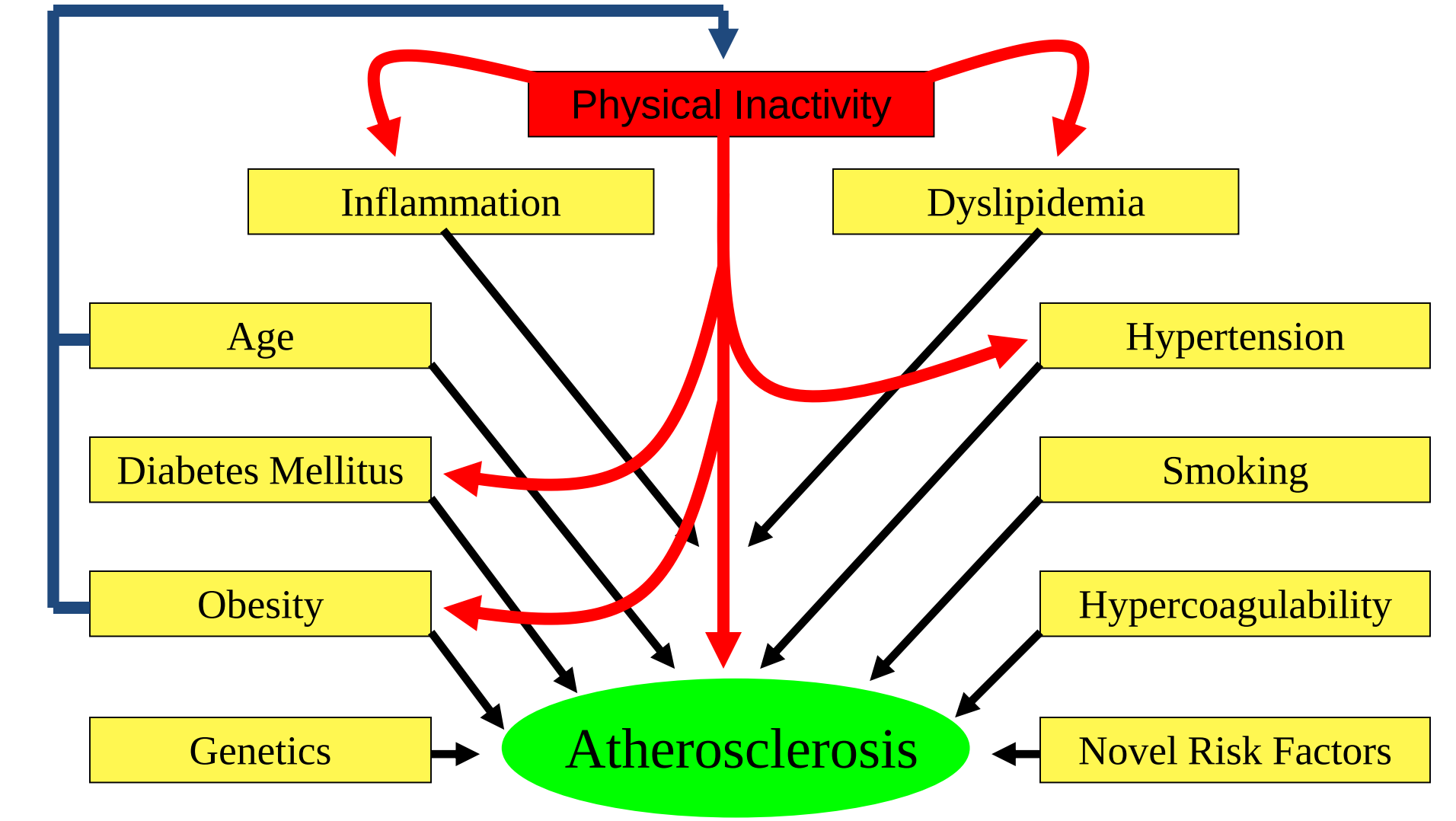
APOE ε4 Copies	prevalence	% with AD	onset age
0	73%	20%	84
1	24%	47%	75
2	3%	91%	68

adapted from Corder et al, *Science* 1993

Sedentary is the new SMOKING



Adverse Effects of Physical Inactivity



EXERT Study

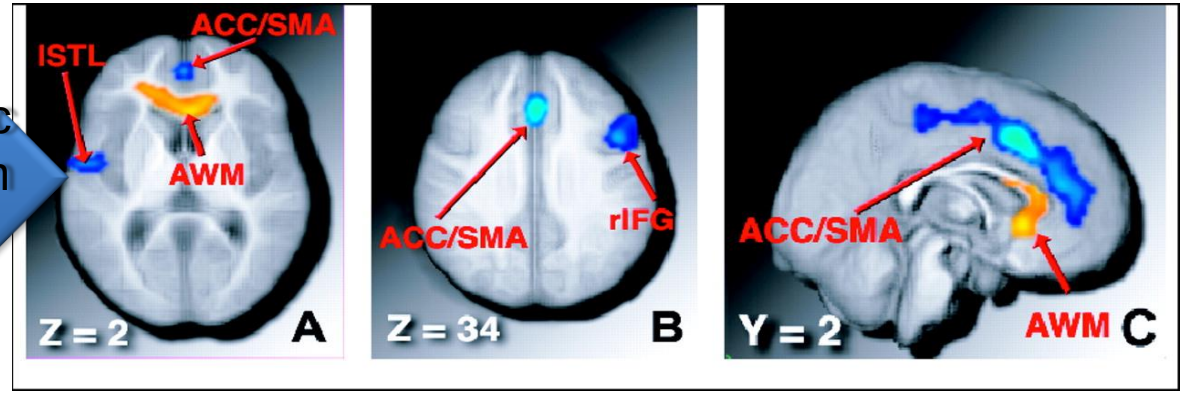
- Background: Exercise known to increase vascular function, improve insulin sensitivity, may increase cognitive resilience and prevent cognitive decline and dementia

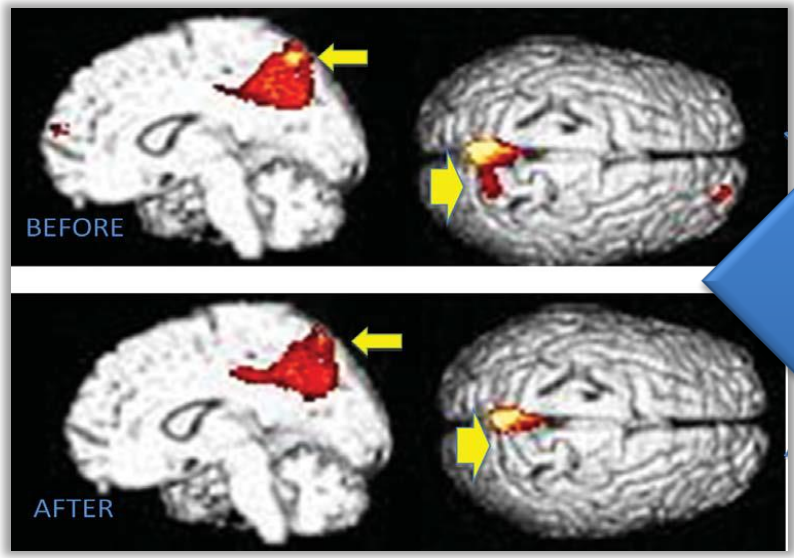
- Intervention: YMCA, exercise 45 minutes per session, 4 times per week; supervision twice per week for 12 months, and independent exercise for the last 6 months of the study
  - Aerobic exercise: 70-80% of maximum heart rate for 30 minutes of each 45 minute session
  - Stretching, Balance, Range of Motion exercise: 30% of maximum heart rate for 45 minutes per session

https://www.exertstudy.org/

Aerobic Exercise and Brain Function in Older Adults

In healthy adults, brain volume increased with 6 months of aerobic exercise (colors=areas showing an increase) (Colcombe 2006)





In adults at increased risk for Alzheimer's dementia (e.g., with mild cognitive impairment), exercise increased brain metabolic activity in regions that are first affected by the disease (Porto 2016)

Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)

Partnership between Rush University Medical Center and Harvard School of Public Health

Three-year research study that compares two weight loss diets and their effects on brain health and cognitive decline.

Lifestyle and behavioral changes to help you lose weight and live healthier.

Rigorous compliance = 53% reduction in Alzheimers Disease

Moderately strong compliance = 35% reduction

Much easier than other research-based healthful diets

Multiple Failed Clinical Trials

The need for early intervention

- Requires criteria for Alzheimer's other than dementia, which is a late symptom.
- Redefine a research diagnosis through use of Biomarkers
- Amyloid imaging
  - Abeta42 in cerebrospinal fluid
- Validate surrogate markers for progression.
  - In both the symptomatic & presymptomatic stages of AD

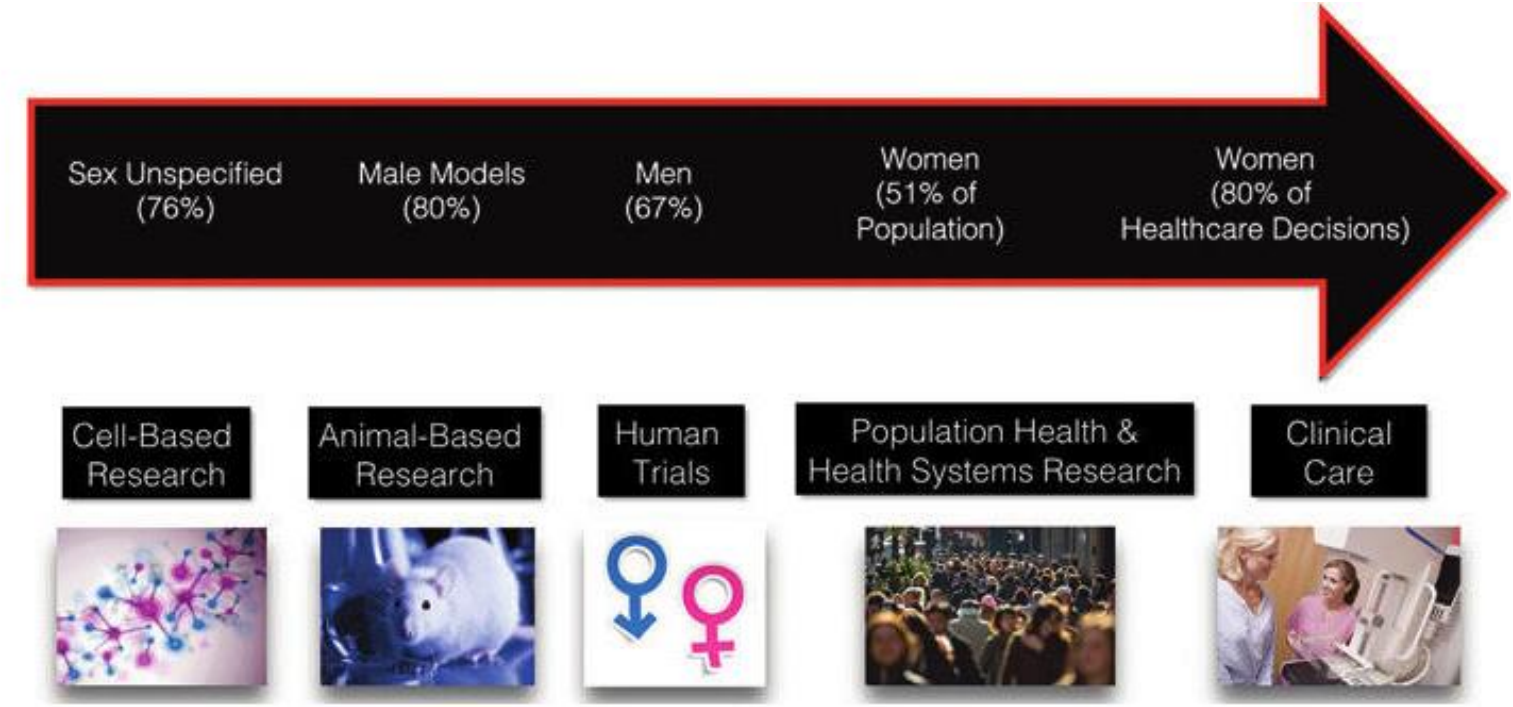
The need for safety & tolerability data

- To evaluate investigational AD-modifying treatments in presymptomatic AD trials
- ***Evaluate Sex differences and report findings***

Genetics and Considerations

- Predictive value? How are we communicating this?
  - Will the condition develop? When?
  - How severe? Will interventions make a difference?
  - Direct implications for family members-Ethical, legal and social issues

Bias in the Research-Pipeline



Song et al, *J of WH* (2015)

XXY | Sex and Gender MEDICAL EDUCATION SUMMIT

SEX AND GENDER

Sex is a biological variable defined by characteristics encoded in DNA, such as reproductive organs.

Gender refers to social, cultural, and psychological traits linked to human males and females through social context.

Sex, gender, and their **interactions** can all influence molecular and cellular processes, clinical characteristics, and health and disease outcomes.

nature

NIH to balance sex in cell and animal studies

Janine A. Clayton and **Francis S. Collins** unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

May 15, 2014

NIH Takes Steps to Address Sex Differences in Preclinical Research

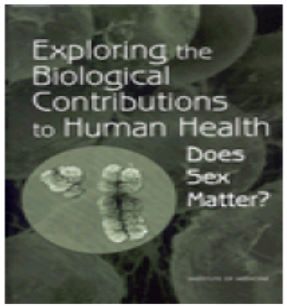
May 14, 2014

Over the past two decades, we have learned a great deal about how men and women respond differently to medications. This knowledge came after a concerted effort in the early '90s to increase the number of women in NIH-funded clinical research.

Today, just over half of NIH-funded clinical research participants are women. Unfortunately, experimental design in cell and animal research has not always followed suit. An over-reliance on male animals, and neglect of attention to the sex of cells, can lead to neglect of key sex differences that should be guiding clinical studies, and ultimately, clinical practice. NIH is taking action to address this shortfall as outlined by Janine A. Clayton, M.D., Director of the NIH Office of Research on Women's Health, and me in the *Nature* Comment below.

Francis S. Collins, M.D., Ph.D. Director, National Institutes of Health

The Evolution of Sex & Gender Medicine from Women's Health Research



Exploring the Biological Contributions to Human Health: Does Sex Matter?

Theresa M. Wizemann and Mary-Lou Pardue, Editors, Committee on Understanding the Biology of Sex and Gender Differences, Board on Health Sciences Policy
ISBN: 0-309-51190-9, 288 pages, 6 x 9, (2001)

In recent years, considerable attention has been given to the differences and similarities between females and males (1) at the *societal* level by researchers evaluating how individual behaviors, lifestyles, and surroundings affect one's biological development and health and (2) at the level of the *whole organism* by clinicians and applied researchers investigating the component organs and systems of humans. However, scientists have paid much less attention to the direct and intentional study of these differences at the basic *cellular* and *molecular* levels. Where data are available, they have often been a by-product of other areas of research. Historically, the research community assumed that beyond the reproductive system such differences do not exist or are not relevant.

Some critical questions:

*How can information on sex differences be **translated** into preventive, diagnostic, and therapeutic practice?

*How can the new knowledge about and understanding of biological sex differences and similarities most effectively be used to **positively affect patient outcomes and improve health and health care?**

Tips for Preserving Cognitive Function

- ……eat a healthier diet!
- …… get MOVING !
- …….sleep!
- …….reduce stress!
- …….improve social engagements!

THANK YOU!