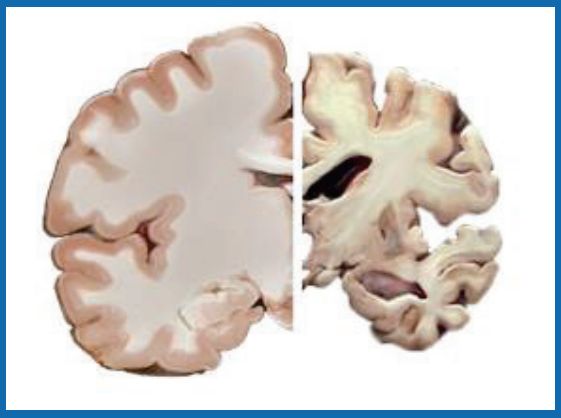
UCLA Health

Kathleen Demarest Tingus, PhD
Director, Neurodegeneration Track
Associate Professor of Neurology and Psychiatry
Semel Institute for Neuroscience and Human Behavior
David Geffen School of Medicine at UCLA

Alexander J. Steiner, PsyD
Postdoctoral Fellow, Neurodegeneration Track
Semel Institute for Neuroscience and Human Behavior at UCLA

Untangling Dementia



Outline

- Staggering Statistics of Dementia
- Normal aging versus Dementia
- Leading causes of Memory Loss and Dementia
- Basic neuroscience of Alzheimer's dementia (AD)
- Risk factors for AD
- Prevention and lowering risk of AD
- Current FDA approved treatments for AD
- Recent advances in the field of AD research
- Clinical trials
- Caregiving Resources

UCLA Health

Staggering Statistics

- 5.5 million Americans are currently living with AD
- 50 million worldwide with dementia, including AD
- AD is the leading cause of dementia among older adults
- The percentage of people with AD increases with age:
  - 3% of people ages 65-74 are diagnosed with AD
  - 17% of people age 75-84
  - 32% of people age 85 and older

Baby Boomers

The number of Americans with AD is expected to triple by 2050 to 16 million

The number of Americans age 65 and older is projected to grow from 53 million in 2018 to 88 million in 2050

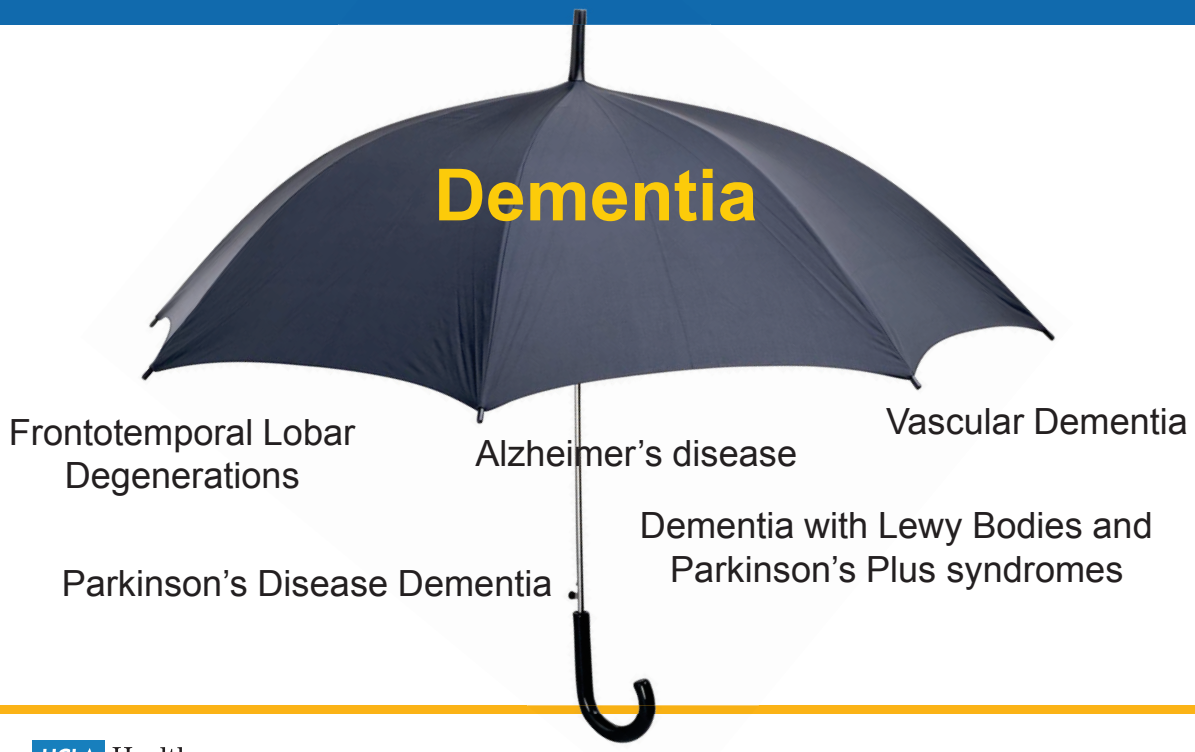
By 2050, the number of Americans age 85+ will quadruple to 21 million. 30-40% in this age group will suffer from AD

More Staggering Statistics

- In 2017, Americans provided 18.4 billion hours of unpaid care to people with AD and other dementias
- The total lifetime cost of care for someone with dementia (including Medicare, Medicaid, out-of-pocket expenditures, and the value of informal care) was estimated at $341,840 in 2017 dollars.
- In 2018, Medicare and Medicaid are expected to cover $186 billion, or 67% of the total health care and long-term care payment for people with AD or other dementias.

National Institute on Aging, 2019 Alzheimer's Disease Fact Sheet

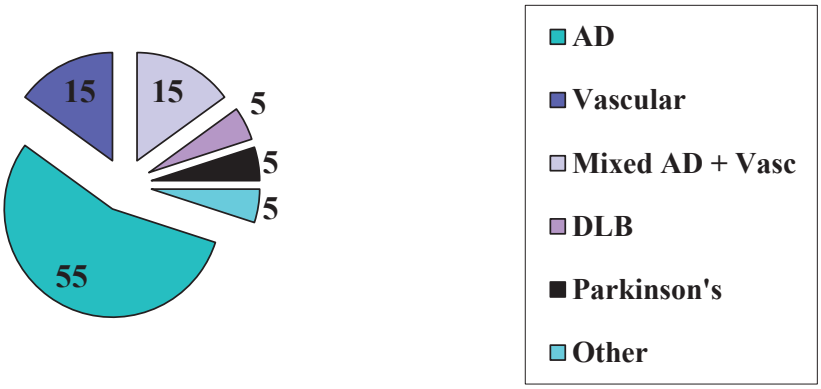
What is Dementia?



UCLA Health

Leading Causes of Dementia

Alzheimer's disease (AD) represents 55-70% of all dementia cases



Nomenclature Defined

DSM-IV (1994)		DSM-5 (2013)
Dementia Disorder	→	Major Neurocognitive
Cognitive Disorder NOS	→	Mild Neurocognitive Disorder

Normal Aging and Changes in Cognition

- Slower thinking and processing speed
- Difficulty in retrieving information (names, words)
- Increased reliance on memory cues
- Sensory declines can impact learning (vision, hearing)

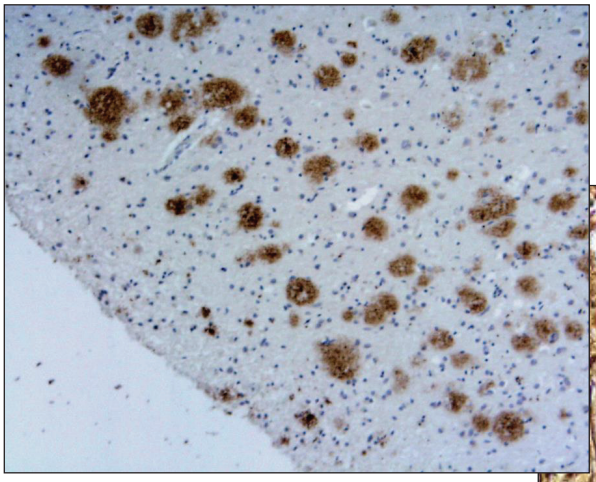
When to Worry

Typical Age-Related Changes	Signs of AD
Sometimes searching for a word	Difficulty having a conversation or frequent word errors
Misplacing things from time to time	Losing things and being unable to retrace steps to find them
Increasing reliance on maps to navigate to new places	Getting lost in familiar locations
Missing a monthly payment	Being unable to manage a budget
Forgetting you told your friend a story and repeating it	Repeating statements or questions within a short period of time

Possible Causes of Memory Loss

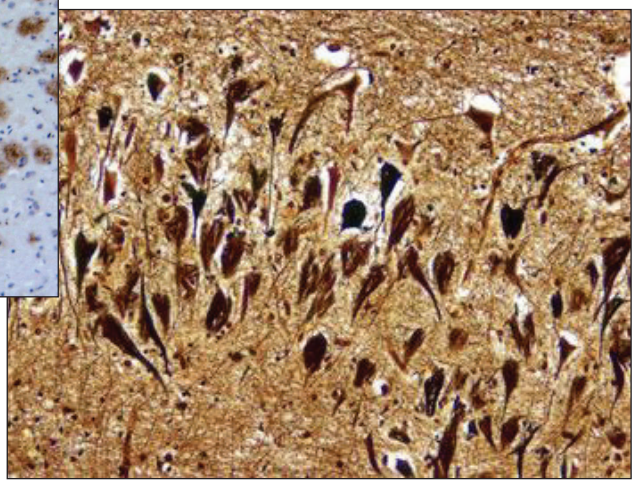
- Normal aging process
- Medication effects
- Depression, anxiety
- Vitamin B12 deficiency
- UTI
- Sleep disturbances (OSA, RBD)
- Severe dehydration
- Hypothyroidism
- Stroke and cerebrovascular disease
- Mild TBI or head injury

Alzheimer's Disease (AD)



Plaques

Tangles



UCLA Health

The Amyloid Cascade hypothesis of AD

- Accumulation of Aβ plaques that dysregulate synaptic and neuronal function
- Intracellular conditions lead to formation of neurofibrillary tangles
- Plaques and tangles lead to neuronal death and further compromise of neurotransmitter function
- Loss of cholinergic neurons in the basal forebrain is hypothesized to create a cholinergic deficit contributing to short-term memory loss in AD

20 years

or more before symptoms appear,

the brain changes of Alzheimer's may begin

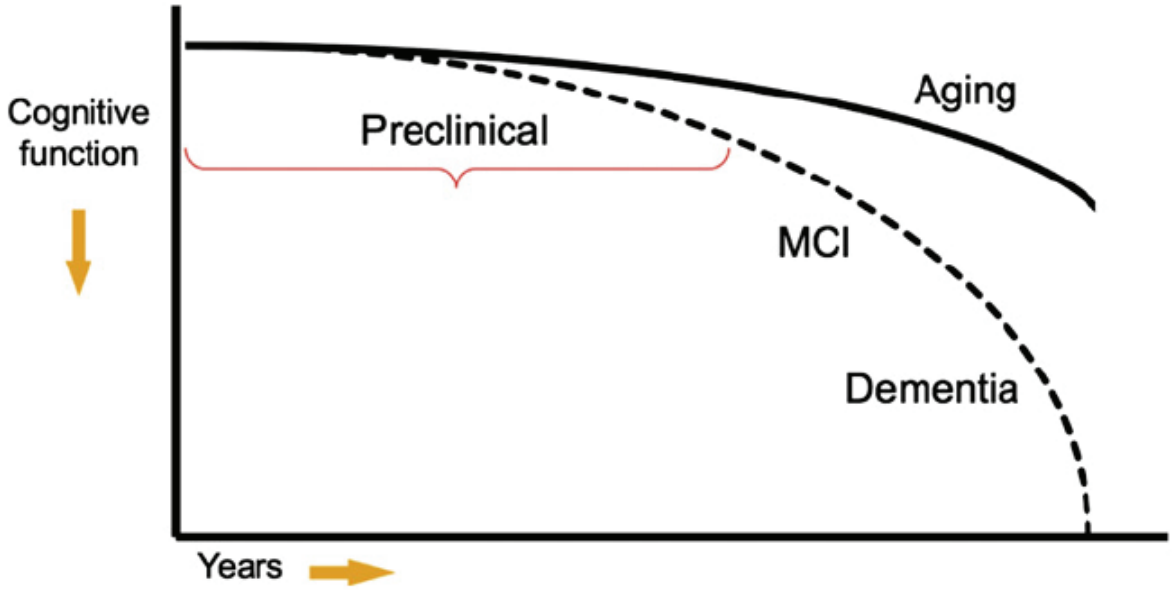
AD: Onset, Course, and Duration

- Late onset AD (age 65 and older)
- Early onset AD (prior to age 65) represents less than 10 percent of all people with AD. Approximately 200,000 Americans under the age of 65 have early onset AD.

- Course – Slow, gradual, relentless progression
- Duration of disease – 8 to 12 years from diagnosis

Stages of Alzheimer's disease: Preclinical

- AD is an insidious neurodegenerative disorder



UCLA Health

Sperling R et al. Alzheimer's & Dementia. 2011

Stages of Alzheimer's disease: Mild

- Mild Cognitive Impairment (MCI)
  - Short term memory
  - Language
  - Visuospatial
- Loss of olfaction (anosmia)
- Impaired awareness (anosognosia)
- Depression and anxiety

Stages of Alzheimer's disease: Moderate

- Densely amnestic
- Losses in long term memory
- More severe language loss, paucity of speech
- Wandering, disorientation
- Declines in basic ADLs
- Dependence in instrumental ADLs
- Personality and behavior changes

Stages of Alzheimer's disease: Severe

- Loss of long term memory
- Severely impaired language, mute
- Motor functions impaired
- Loss of continence
- Dysphagia → pneumonia

Risk Factors for AD

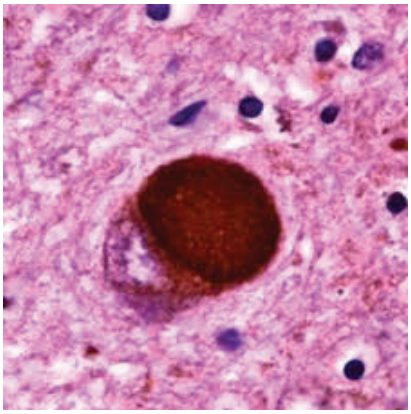
- Age
- Family History
- Apolipoprotein E ε4 genotype
- Diabetes, hypertension, hypercholesterolemia
- Obesity
- Traumatic brain injury (TBI)
- Low education level
- Gender

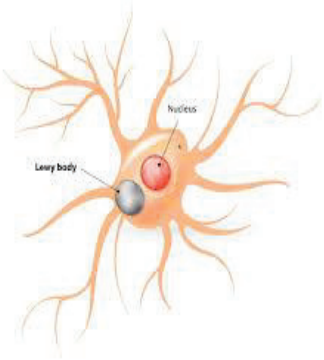
Genetics

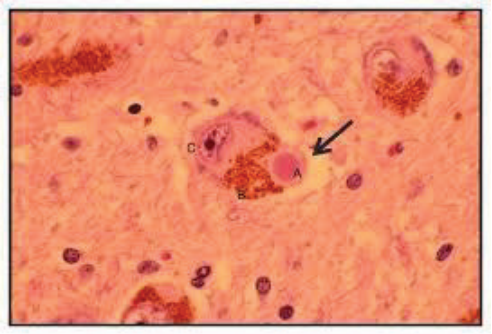
APOE genotype

- We all inherit one APOE gene from each parent.
- The APOE gene helps make proteins that carry cholesterol in the bloodstream
- The APOE gene comes in 3 alleles
  - ApoE ε2 decreases risk (10-20% of individuals have at least one e2)
  - ApoE ε3 plays a neutral role in the disease (Most common. 60% 3,3)
  - ApoE ε4 increases risk (2% 4,4)
    - One ε4 allele = 3 times the risk of developing AD
    - Two ε4 alleles = 8-12 times the risk of developing AD

Dementia with Lewy Bodies







DLB Statistics

- Affects approximately 1.4 million people in the USA.
- Onset typically begins at age 50 or older
- Affects slightly more men than women.
- Course is progressive, marked fluctuations
- Duration lasts 5 to 8 years from diagnosis to death (ranges from 2 to 20).

DLB Core Clinical Symptoms

McKeith Criteria – June, 2017

- Parkinsonism
- Visual hallucinations – 80%
- Fluctuations in mental clarity
- REM sleep behavior disorder

DLB Supportive Clinical Symptoms

- Falls, fainting
- Autonomic Nervous System symptoms – Blood pressure fluctuations, incontinence, constipation
- Changes in personality and mood (depression, anxiety, apathy)
- Loss of olfaction

Differentiating DLB from Parkinson's disease

- Both DLB and PD are considered Lewy Body Diseases
- "One year rule"
- Early cognitive involvement in DLB
- Stronger response to dopaminergic agents in PD
- Neuropsychological profiles similar

Reducing your risk of AD/Dementia

- Stop aging
- Choose the right parents (genes)
- Eat a healthy (Mediterranean) diet
- Control hypertension and high cholesterol
- Keep your mind active
- Get regular exercise
- Protect your brain (wear a seatbelt, helmet)

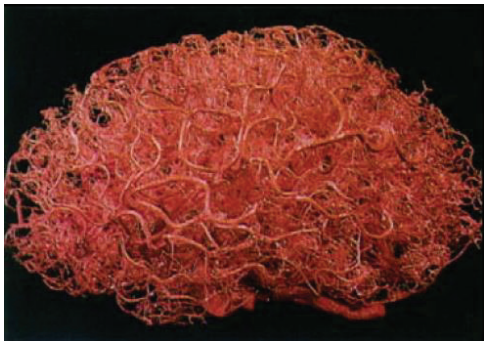
Super Agers

Taking a proactive approach to prevention

- Modify risks
  - Reduce risks for heart and cerebrovascular disease
  - Healthy lifestyle
    - Diet
    - Exercise
    - Sufficient sleep
    - Reduce stress and optimize well-being
    - Smoking cessation
    - Some supplements
  - Cognitive stimulation

The Heart-Brain Relationship

- Your brain accounts for 2% of your total body weight
- Your brain uses 20% of your blood oxygen/sugar
- Reduced blood flow to the brain results in significant damage to neurons.

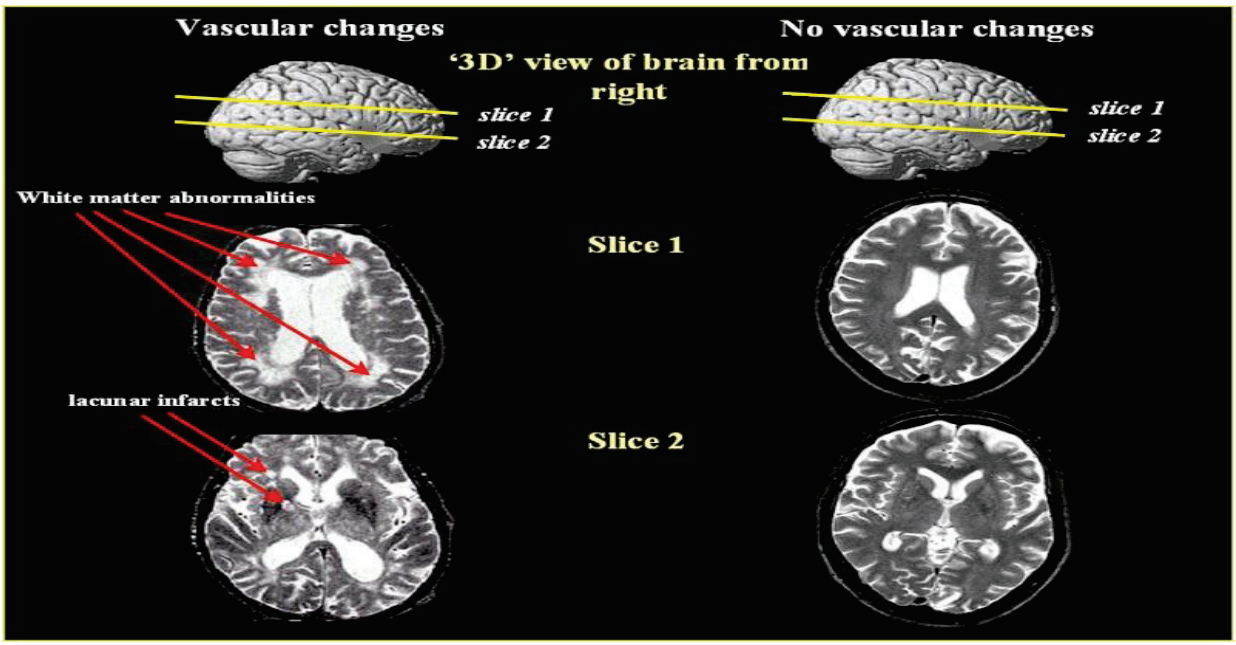


Cardiovascular Conditions Increase Risk for Alzheimer's disease

- Cardiovascular disease
- Hypertension
- Stroke
- Diabetes
- High cholesterol

Lowering your risk for/controlling these conditions can lower your risk of AD

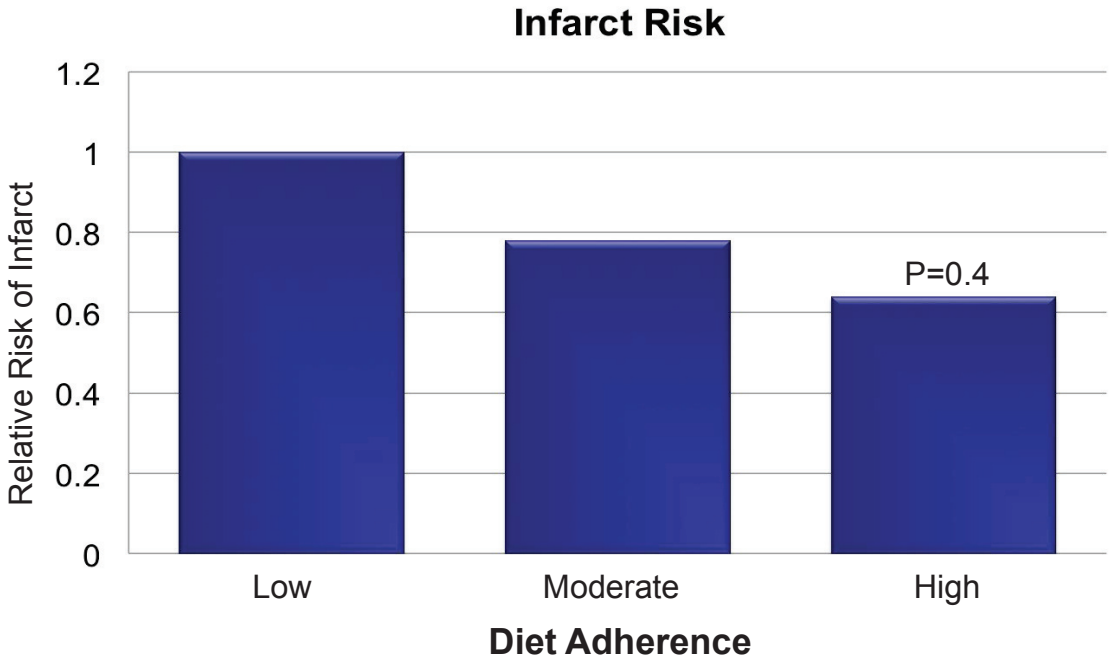
Cerebrovascular Changes on MRI



UCLA Health

Courtesy of UCSF Memory and Aging Center

Mediterranean Diet Lowers Risk for Cerebral Infarct



UCLA Health

Scarmeas et al. (2011)

Mediterranean Shopping List

- **Fish** (omega-3 fatty acids; salmon, herring, mackerel)
- **Fruits and vegetables** (antioxidants and anti-inflammatories; leafy greens like kale, spinach, brussel sprouts, and collard greens, deeply hued produce like eggplant, bell peppers, tomatoes, blue berries, strawberries, and blackberries
- **Olive oil** (monounsaturated fat; extra virgin)
- **Nuts** (FDA recommends 1.5 oz/d; walnuts, pine nuts, pistachios, almonds)
- **Beans** (red kidney, pinto)
- **Red wine** (moderate consumption – no more than 1-2 glasses per day)

Cognitive Activity in Older Persons

- Cognitively inactive persons over the age of 65 are 2.6 times more likely to develop AD
- Social network size modifies the association between disease pathology and cognitive function
  - Assuming equal pathology, a person with a greater social network will have better cognitive function

Bennett et al. (2006); Wilson et al. (2007)

Mentally Stimulating/Leisure Activities

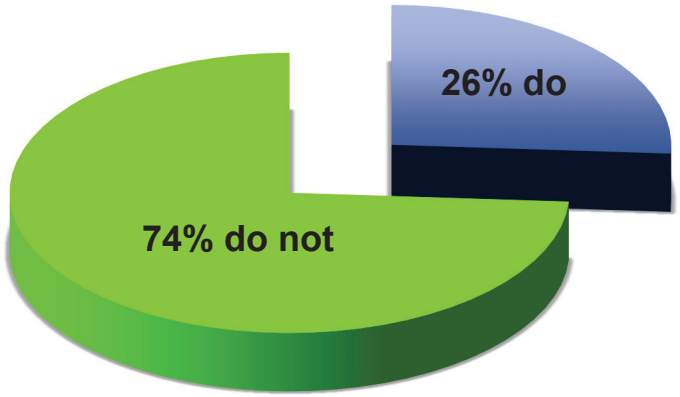
- Puzzles
  - Crossword
  - Sudoku
- Traveling
- Knitting
- Gardening
- Reading/Book clubs
- Movie clubs
- Board games
  - Checkers
  - Chess
- Musical Instruments
- Visiting Museums
- Attend plays

Frequent Exercise Lowers Risk for:

- Diabetes
- Hypertension
- Hypercholesterolemia
- Obesity

30 Minutes of Moderate Exercise is Recommended for Adults

% American adults who get the recommended 30 minutes of moderate exercise most days of the week



UCLA Health

Hillman et al. (2008); Colcombe & Kramer (2003)

Being active is good for you!

- Many data support the importance of physical activity and its ability to lower risk for dementia
- Framingham Study
  - Moderate to heavy physical activity is associated with a reduced risk for dementia

UCLA Health

Z.S. Tan presentation at 2010 Alzheimer's Association International Conference on Alzheimer's Disease

Effects of exercise on the brain

- Dysregulation of hippocampal neurogenesis → cognitive difficulties
- Chronic neuroinflammation can inhibit hippocampal neurogenesis
- Neuroinflammation → to cognitive decline.
- Exercise = potent pro-neurogenic and pro-cognitive effects
- Exercise likely has a number of anti-inflammatory effects in the brain

Ryan & Nolan (2016)

Is sleep important?

- The role of deep sleep in clearing neurotoxins and proteins has been well established in animal models
- Researchers at Washington University in St. Louis published findings that among cognitively normal older adults, non-rapid eye movement (NREM) sleep negatively correlated with tau pathology and Aβ deposition in several brain regions.
- Findings further suggested that alterations in NREM slow wave activity might be able to discriminate tau pathology and cognitive impairment either before or during the prodromal symptomatic stage of AD

Lucey et al. (2019)

Gender

- Almost 2/3rds of Americans with AD are women
  - 3.4 million women versus 2.0 million men
- ApoE interaction
  - ApoE e4 genotype may have a stronger association with AD in women than in men.
  - Some evidence suggests that it may be due to an interaction between the ApoE e4 genotype and estrogen.
- Survival bias?

Risk by Ethnicity/Race

- Older Af-Am ~ 2x more likely to have AD and other dementias vs older whites.
- Hispanics are ~ 1.5 x to have AD and other dementias vs older whites.
- All time prevalence rates per capita are as follows:

  Af-AM, Hispanic, white, Asian.
- Not enough data for estimates in other ethnic groups

Alz Assn 2017 Facts and Figures

Reasons for Differences in Prevalence

- Health conditions
  - Higher cardiovascular in Af-Am and Hispanic
- Racial differences in childhood, social and economic adversity and adulthood SES
- Lifestyle differences

Potter et al. (2009); Gurland et al. (1999); Samper-Ternent et al. (2012); Zhang et al. (2016)

Alz Assn 2017 Facts and Figures

Courtesy Dr. Linda Ercoli

Head Trauma (Traumatic Brain Injury)

- Persons who experience head trauma are more likely to develop AD later in life
  - May interact with genotype
  - Injury and recovery may increase Tau and Aβ production

Heyman et al. (1984); Mayeux et al. (1991); Brody et al. (2008)

Alzheimer's Care

- Early identification is critical
  - We cannot reverse losses
  - Goal is prevention, or slowing the amyloid process
  - Rule out other causes of cognitive impairment
  - Treat reversible causes
- Work with appropriate physicians
  - Primary care/Geriatrician
  - Psychiatrist/Geriatric Psychiatrist
  - Neurologist
  - Neuropsychologist

Why diagnose if no cure?

Slow disease progression

Advanced directives, financial and legal planning

Education of patient and loved ones

Address potential safety issues before they arise

Allow time to create support networks

Participation in clinical trials

Research Has Changed Alzheimer's Diagnosis

- Increased confidence
- Ability to diagnose earlier
- Biomarkers of Alzheimer's disease

Biomarkers

Definition: a biological factor that can be measured to indicate the presence or absence of disease, or the risk of developing a disease.

- In AD used to increase or decrease the level of certainty for dx
- Distinguish Alzheimer's dementia from other dementias

- Biomarkers (CSF, Neuroimaging, Genetics?):
  - Amyloid; Low CSF AB42 (amyloid) is early biomarker (some studies show 10 – 20 years prior to clinical symptoms)
  - Neuronal degeneration/injury: High CSF total and P-tau biomarkers in CSF are later symptoms
  - Neuroimaging biomarkers
    - Amyloid, FDG-PET, MRI (particularly volumetric analysis)

Courtesy Dr. Linda Ercoli

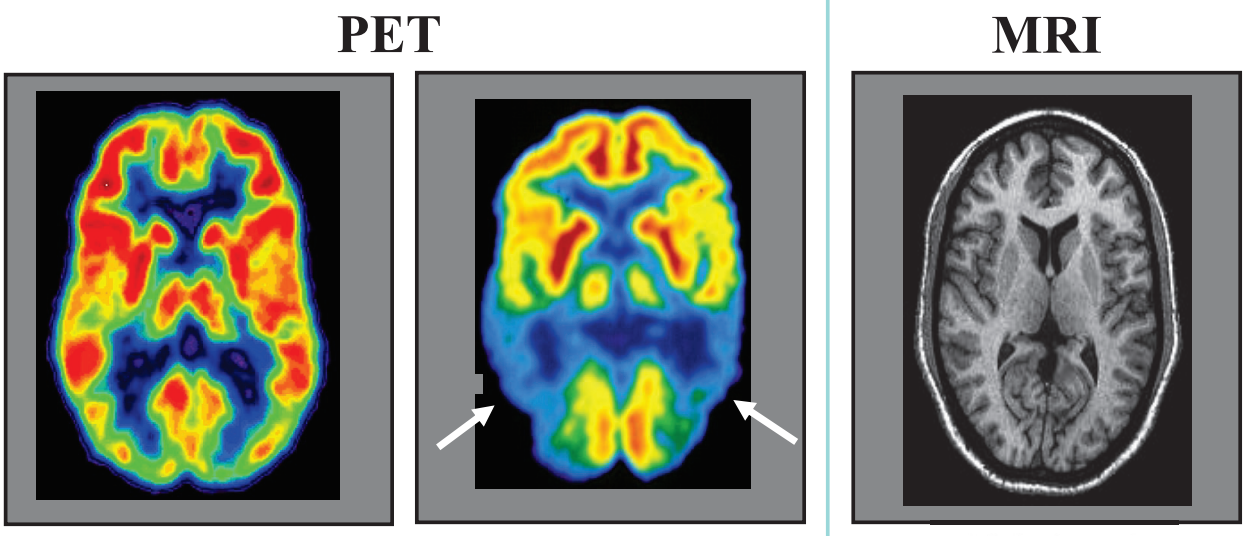
Genetic Considerations for Alzheimer's Disease

- Autosomal dominant forms of AD 1-2%.
  - Rare families have a genetic mutation that causes the disease early in life in 50% of relatives;
  - Presenilin genes (chromosomes 1 and 14)
  - APP gene (chromosome 21)
  - Down Syndrome
  - APOE-4
  - Genome-wide association studies (GWAS) revealed 20 loci potentially involved in AD;
    - rare genes, small effects; potential polygenic causes of AD.

Medway and Morgan (2014); Courtesy Dr. Linda Ercoli

UCLA Health

FDG-PET Study of Alzheimer's Disease

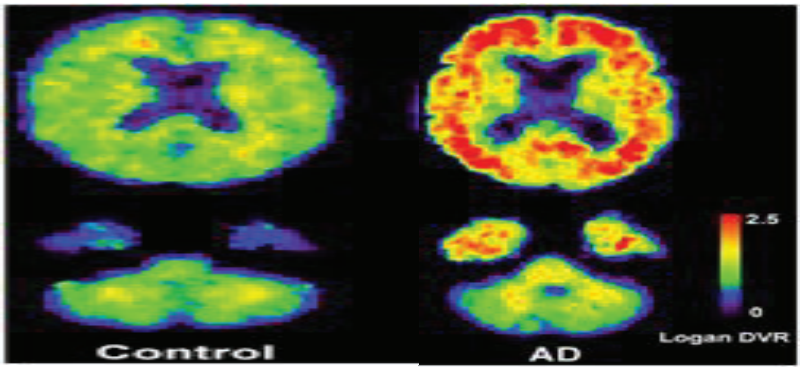


UCLA Health Courtesy of Drs Daniel Silverman, Gary Small, and Michael Phelps, UCLA School of Medicine

Amyloid Positron Emission Tomography(PET)

- Amyvid is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline

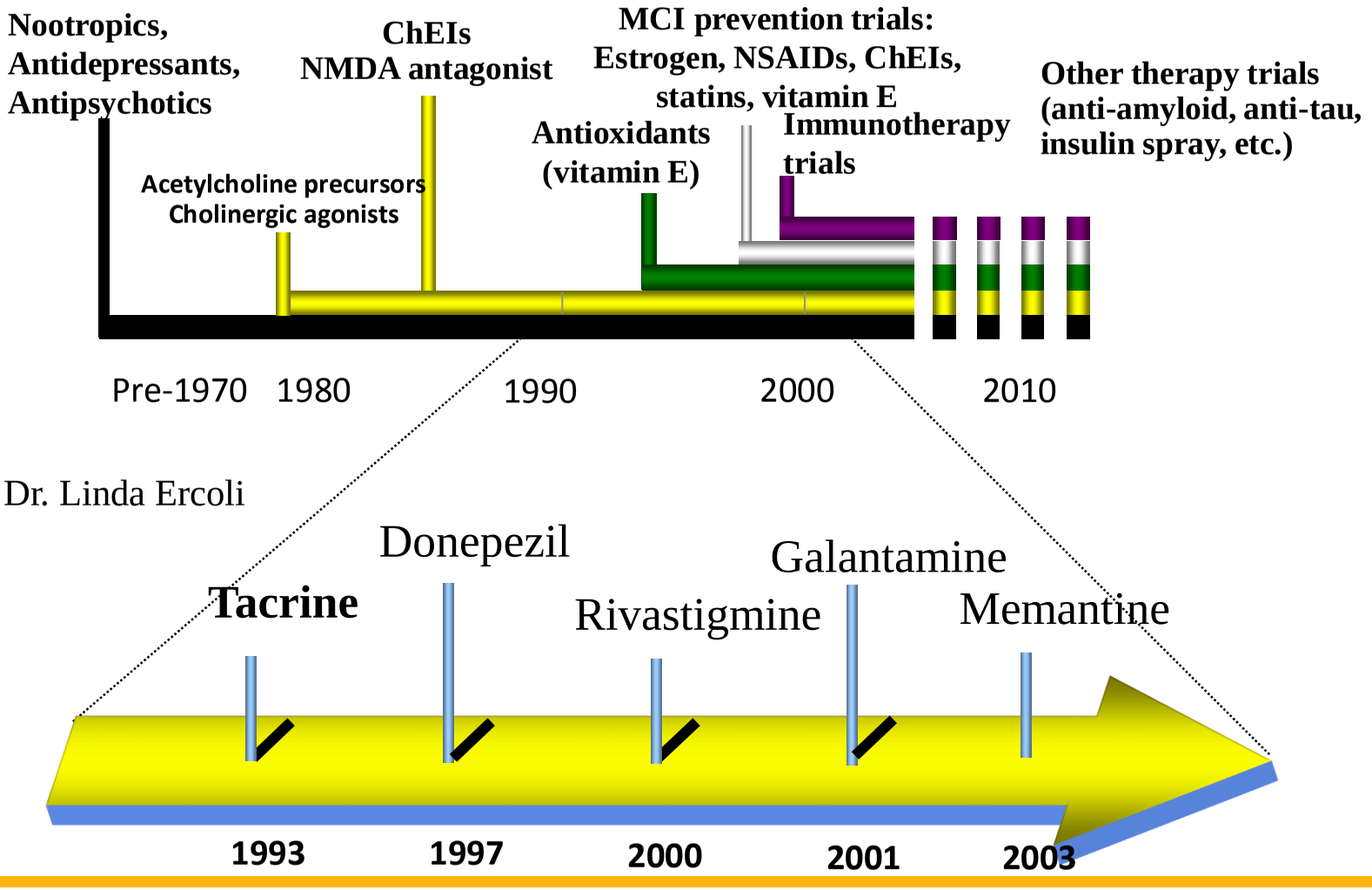
- Does not equate to a diagnosis of AD or other disorder!



FDA Approved AD Treatments

- Aricept® (donepezil)—all stages
- Razadyne® (galantamine)—mild to moderate
- Exelon® (rivastigmine)—mild to moderate
- Namenda® (memantine)—moderate to severe
- Namzaric® (donepezil and memantine)-moderate to severe
- None are approved for use in people with mild cognitive impairment (MCI) or normal memory functioning
- None have been shown to slow the course of Alzheimer's disease

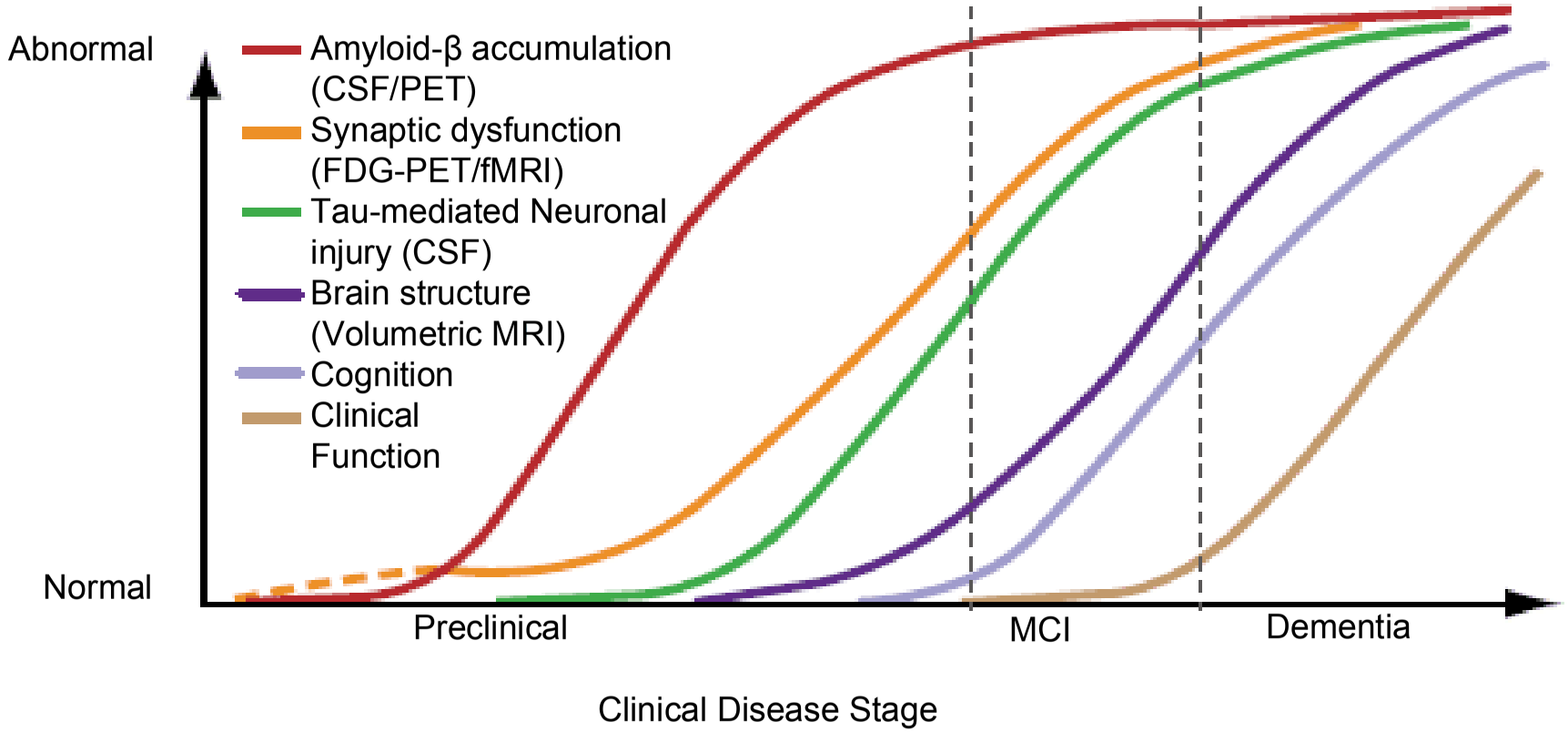
Pharmacologic Therapy for AD: Timeline



Courtesy Dr. Linda Ercoli

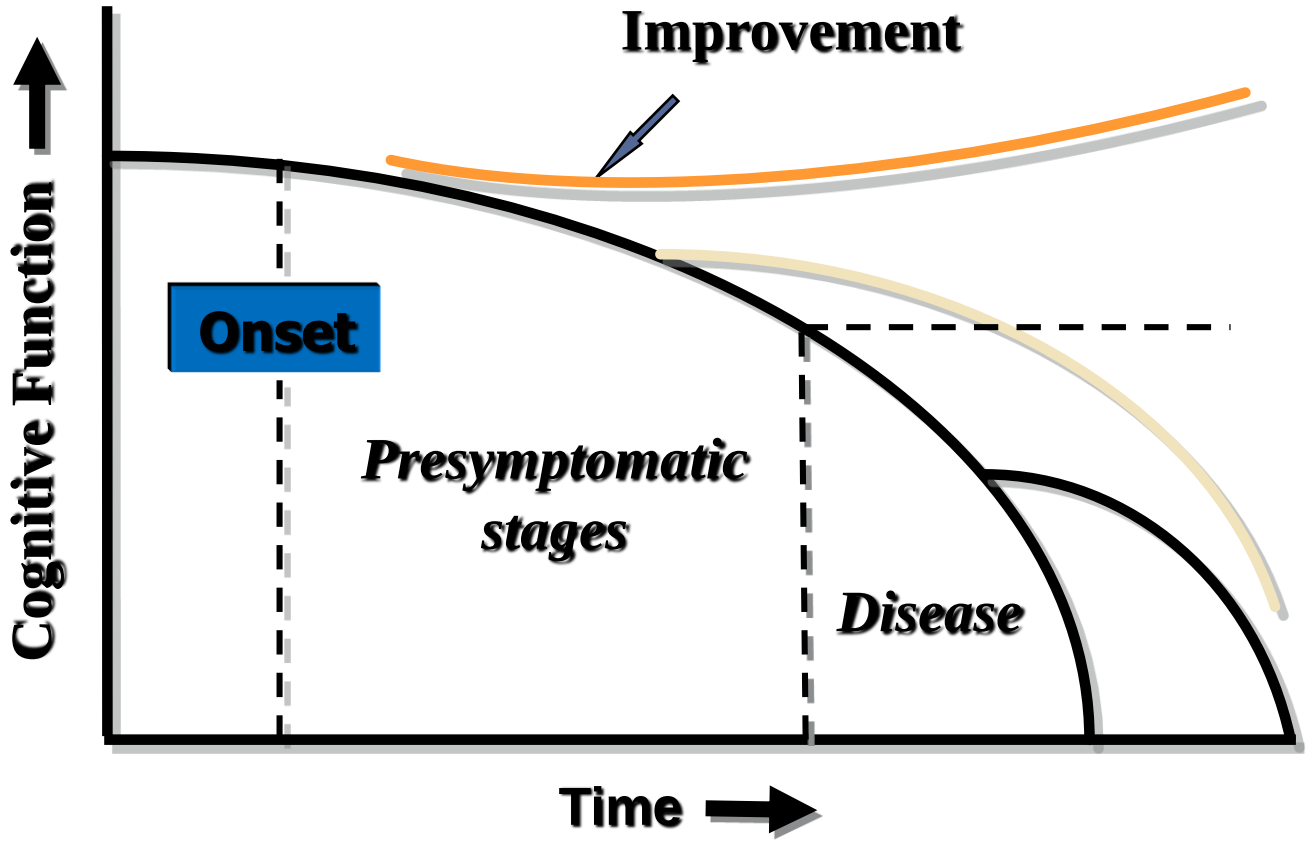
AD = Alzheimer disease; ChEI = cholinesterase inhibitor; NSAID = nonsteroidal antiinflammatory drug

Progression of Pathophysiology Markers and Clinical Syndromes

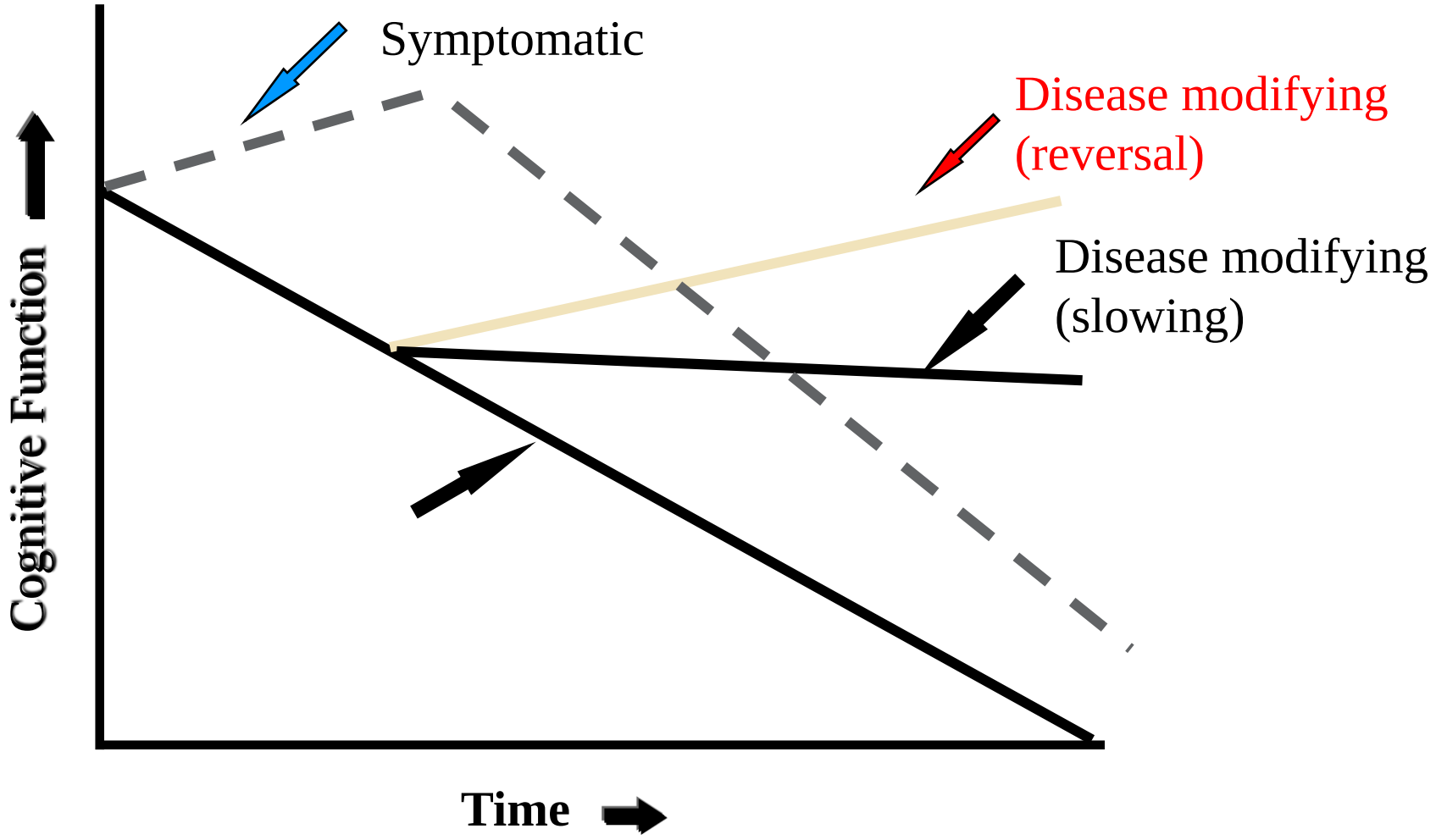


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2819840/

Possible Result of Earlier Treatment



Symptomatic vs. Disease Modifying Treatments



How to Assess Available Information

- Gingko Biloba
- Coconut oil
- Aluminum
- Flu shots
- Many, many more

- Talk to your doctor before you begin any new medication or supplement

Treatment Combinations for AD

- Many clinical trials of single agent therapies have failed to alter disease progression or affect symptoms compared to placebo
- The complex pathophysiology of AD may necessitate combination treatments rather than monotherapy.
- We are now moving to Combination Therapies, which have succeeded in other diseases (HIV and Cancer)
- Need to address more than one target (e.g., Beta amyloid)

Local Clinical Trial Resources

- Easton Center for Alzheimer's Disease Research at UCLA
  - 310-794-6039 www.adc.ucla.edu
- Kagan Institute for Clinical Trials at UCLA
  - 310-794-6191
- www.nia.nih.gov/alzheimers
- clinicaltrials.gov

Caregiving Resources

- Alzheimer's Association

  www.alz.org
- Alzheimer's Disease Education and Referral Center (ADEAR) Family Caregiver Alliance

  www.caregiver.org
- Lewy Body Disease Association

  www.lbda.org