Ginko Biloba and Dementia

Presented by Janelle Morris

NFSC 641

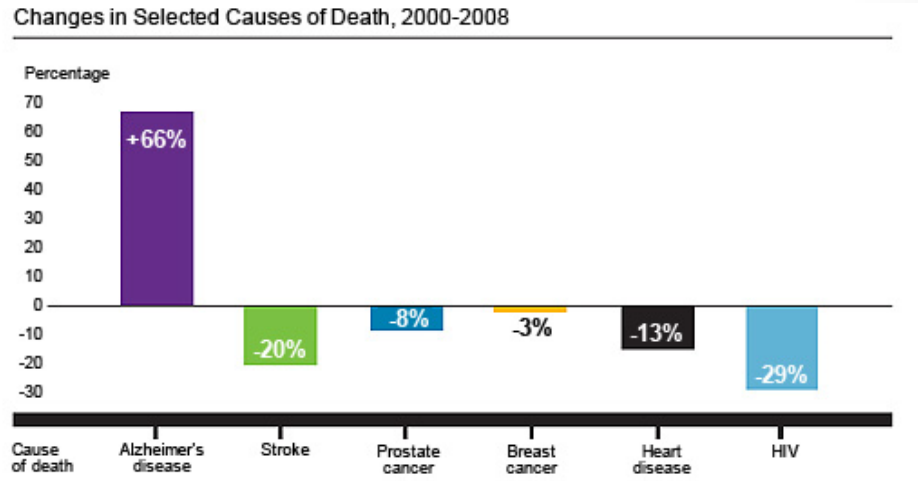
Terms

- **Mild Cognitive Impairment (MCI):** a state of cognitive functioning that is below defined norms, yet does not meet criteria for dementia[8].
- **Dementia**: The general term for conditions that involve memory loss. These conditions may also include impairment in language, judgment, calculation, or problem solving [1].
- **Alzheimer's Disease**: chronic ,progressive, degenerative disease of the brain. The most common form of Dementia, accounting for 60-80% of all cases of dementia.[8]
- **Amyloid Beta**: a part of the amyloid precursor protein found in the insoluble deposits outside neurons, which forms the core of plaques [1].
- **Amyloid Plaques**: cellular deposits found between nerve cells [1].
- **Apo lipoprotein E**: a protein that carries cholesterol in blood and that appears to play a role in brain function [1].
- **Mini Mental State Exam (MMSE):** test used to assess mental function. A health professional asks a patient a series of questions designed to test a range of everyday mental skills. Normal: ≥25 points (out of 30); severe (≤9 points), moderate (10-20 points) or mild (21-24 points)

- **Tau:** Structural protein of microtubules in normal nerve cells. Principle component of paired helical filaments in neurofibrillary tangles[1]
- **Neurofibrillary Tangles:** collections of twisted tau found in the cell bodies of neurons in AD[1]
- **Transthyretin:** involved in beta amyloid transport
- **Secretase**: the enzyme that cuts the amyloid precursor protein and prevents amyloidogenic fragments from being produced
- **Reactive Oxygen Species**: mediators of intracellular communication. Too much can lead to oxidative stress, loss of cell function, and apoptosis
- **Aphagia**: Cannot verbally express preferences[1]
- **Apraxia:** Cannot manipulate utensils and food prior to eating; cannot manipulate food within mouth/swallow[1]
- **Agnosia:** Cannot recognize utensils or food [1]
- **Amnesia:** forgets having eaten; does not recognize need to eat[1]
- **Anorexia:** Lack of desire to eat, with possible psychological basis[1]

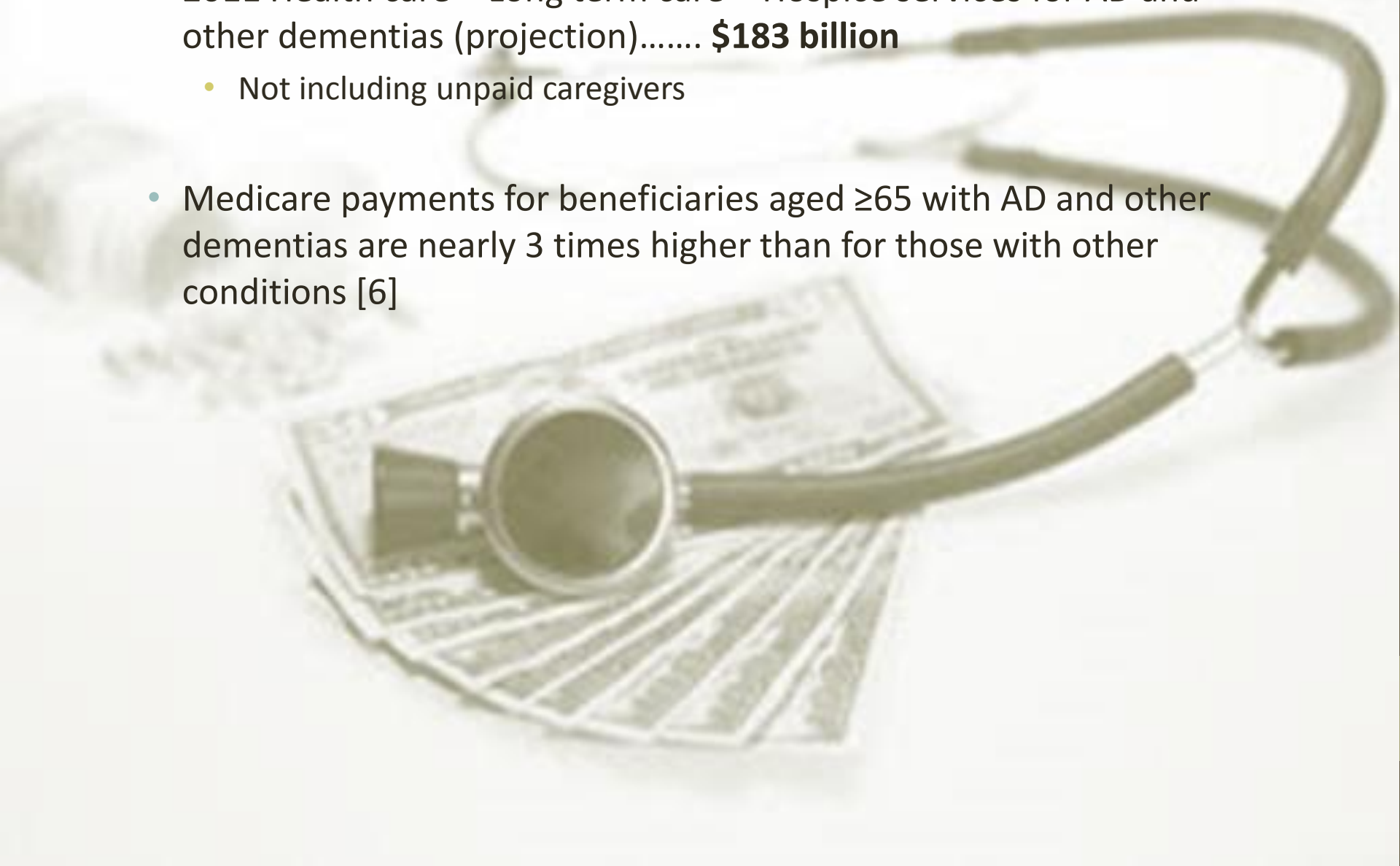
Introduction

- Prevalence
- Alzheimer's Disease Prevalence:
  - 6th leading cause of death in Americans
  - 5th leading cause of death in Americans ≥65 years
  - 2000-2008 Death due to AD increased 66%
  - Currently approximately 5.4 million Americans have AD
  - 200,000 are under age 65 (younger-onset AD population)[6]
- Alzheimer's Disease for the future:
  - Baby Boom generation expected to add 10 million people in coming decades [6]



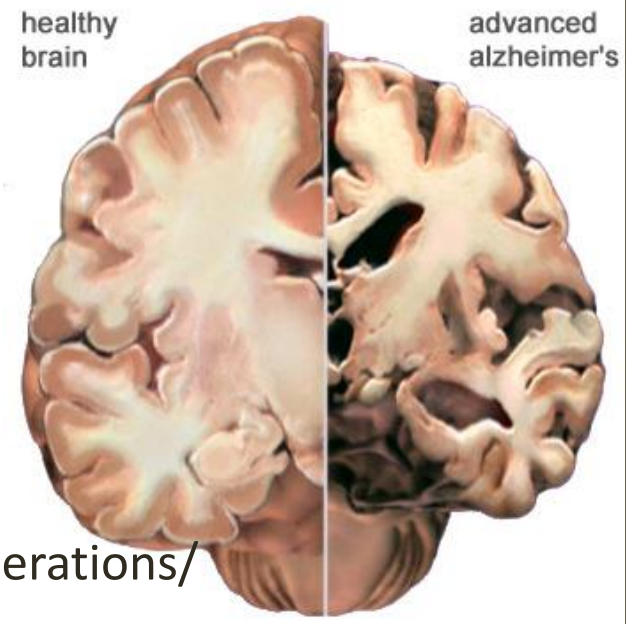
Source: Alzheimer's Association *2011 Alzheimer's Disease Facts and Figures.*

- The Bottom Line
  - 2011 Health care + Long term care + Hospice services for AD and other dementias (projection)……. **$183 billion**
    - Not including unpaid caregivers
  - Medicare payments for beneficiaries aged ≥65 with AD and other dementias are nearly 3 times higher than for those with other conditions [6]



- What is Alzheimer's Disease?

Etiology



- Classification
  - Early-onset: ages 30-60 (least common)
  - Late-onset: 65+ years old
  - Familial: predictably affected two consistent generations/ inherited

- Genetic distinctions
  - Type 1: early-onset, familial
  - Type 2: late-onset, familial
    - Association with abnormalities in apolipoprotein E (apo e4)
    - Occurs in 40% AD people
  - Type 3 & 4: early-onset, familial
    - Different genetic abnormalities which affect amyloid beta protein [6]

Diagnosis

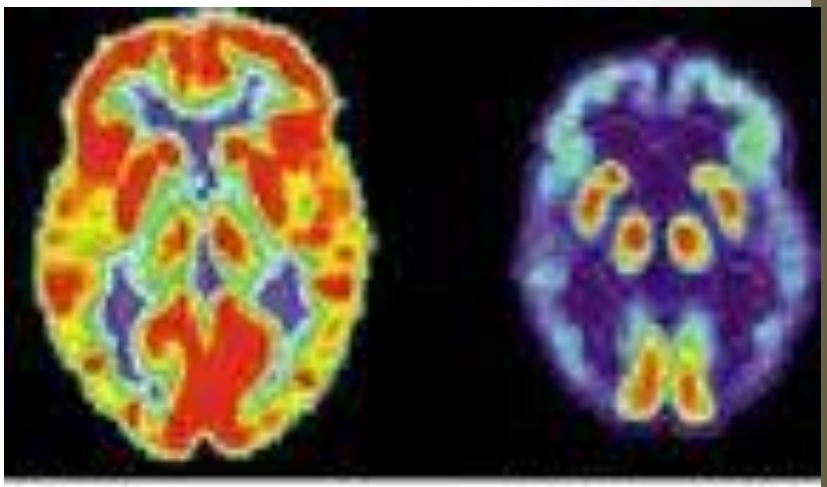
- Current diagnosis: presence of Amyloid-beta plaques and tangles in the cortical areas of the brain at autopsy

1. Family history
2. Mental status test
   - Does the person realize there is a problem?
   - Do they know the date, time, or where they are?
   - Can they remember a short list of words, follow simple directions, do simple calculations?
3. Mini Mental State Exam (MMSE)
4. Lab tests are checked to rule out other diseases

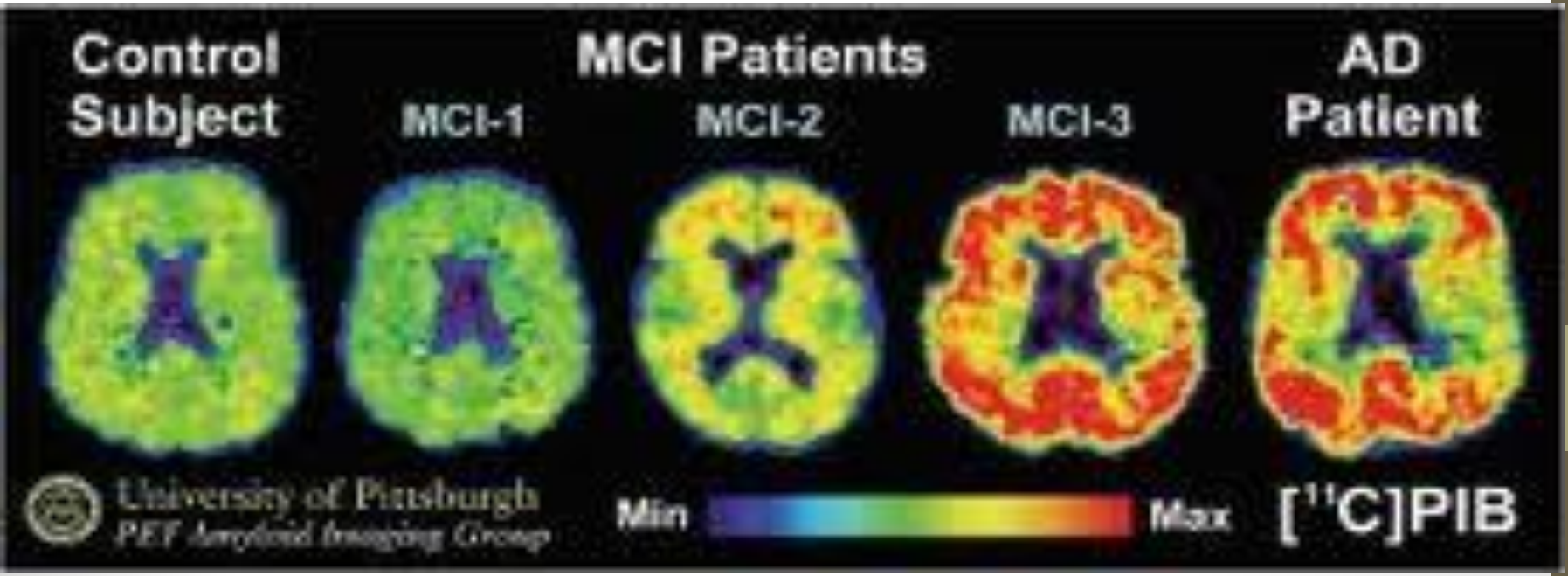
- [6]

5. Neurological Exam
   - Test reflexes
   - Coordination and balance
   - Eye movement
6. Brain Imaging
   - Structure image (MRI)
   - Function image (Pittsburgh compound B)

[6]

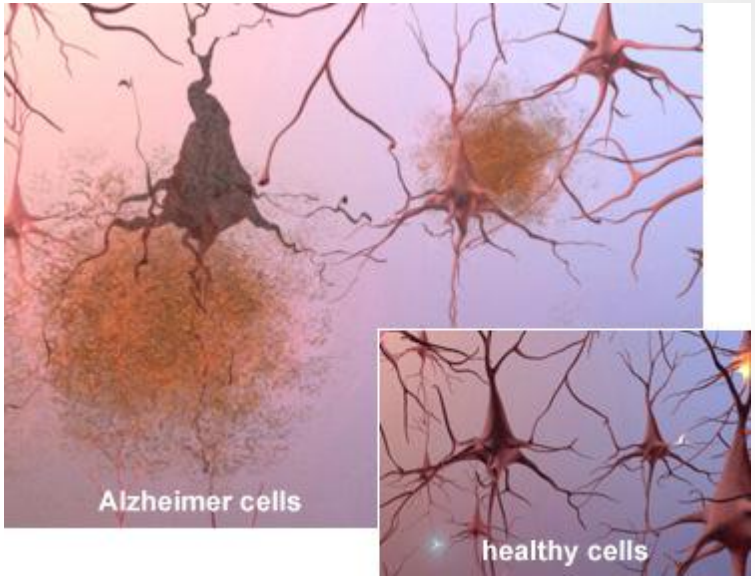


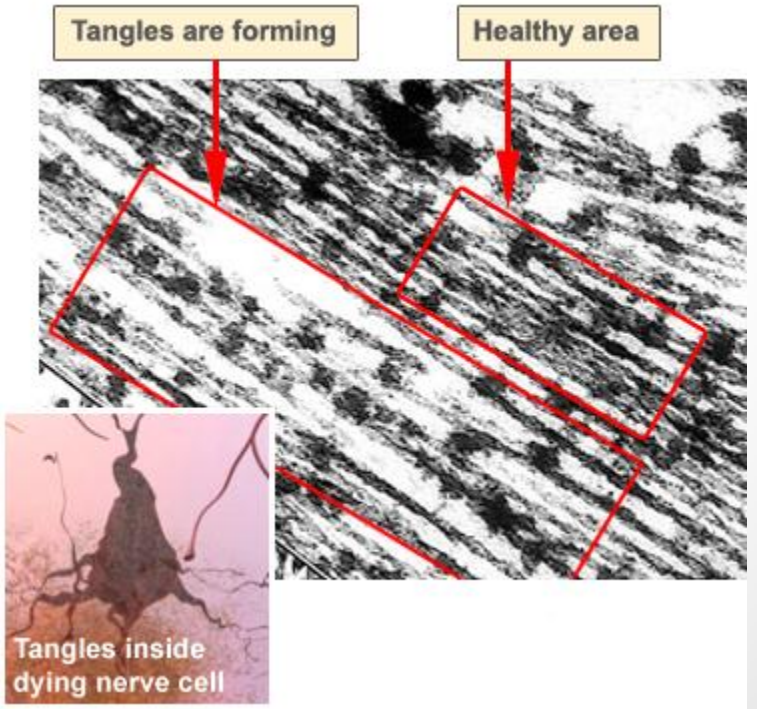
PET scans of normal brain (left) and an Alzheimer's brain. Photo: U.S. National Institute on Aging



Pathophysiology

1. Beta-amyloid precursor proteins develop and amyloid plaques build up
2. Plaques aggregate
3. Neuron function, communication and repair begins to decline
4. Tau protein (structure) forms neurofibrillary tangles in neurons
5. Neurons die





Possible Mechanisms: What Causes Dementia/AD?

- Amyloid Beta Plaque causes inflammatory response
- Oxidative Stress/damage
- Cell degeneration
- Cell synapses decline
- Inflammation

Nutrition

- Nutrition problems with AD include:
  - Aphagia: Cannot verbally express preferences[1]
  - Apraxia: Cannot manipulate utensils and food prior to eating; cannot manipulate food within mouth/swallow[1]
  - Agnosia: Cannot recognize utensils or food [1]
  - Amnesia: forgets having eaten; does not recognize need to eat[1]
  - Anorexia: Lack of desire to eat, with possible psychological basis[1]

Nutrition Goals for Dementia

- Maintain a reasonable weight (BMI 22-27)
- Provide sufficient kcals
- Minimize confusion in the environment:
  - one food at a time, simple place settings, plate should be a different color than the table, add condiments prior to serving
- Offer finger foods
- Strive to maintain independence in self-feeding but provide assistance when patient is unable to maintain adequacy
- Provide alternate opportunities to eat if the patient has difficulty sitting still
  - (ie. Snacks, finger foods)
- Minimize choking/aspiration
  - Adjust texture
- Adequate time allowed per meal
- Maximize food intake during lunch
  - Cognition is usually best [1]

Alzheimer's Prevention

- Fruits and Vegetables[2]
  - Diets high in blueberries and tomatoes may have protective effects
  - Decrease biomarkers of inflammation and oxidative stress
- Exercise[2]
- Ginkgo??

Ginkgo Biloba

- **What is it?**
  - Herbal extract usually taken from the leaf
    - Extracts are sometimes taken from the seed, but these are not well studied
  - Longest living tree species in the world!
- **Standardized Extract: EGb 761**
  - 24% ginkgo-flavone glycosides and 6% terpene lactones (ginkgolides, bilobalide)
- **Food Sources**
  - Capsules
  - Tablets
  - Liquid extracts
  - Dried leaves for tea

- **Why take it (claims)?**
  - Memory disorders (Alzheimer's)
  - Conditions which may be due to reduced blood flow to the brain
  - Thinking disorders related to Lyme disease and depression
  - Sexual performance problems
  - Reverse the sexual performance problems that can accompany taking certain antidepressants called SSRIs
  - Eye problems
  - Asthma and Bronchitis
    - Prescribed as early as 2600 bce
  - Improving thinking in young people
    - Improve thinking skills in healthy young to middle-aged people
    - Improve memory and speed of mental processing in people without memory loss

- Are there interactions with medications?
  - Anticoagulant / Antiplatelet drugs: Ginkgo and can slow blood clotting; Combining Ginkgo with other blood clotting medications can increase the chance of bruising and bleeding.
    - Ie. Ibuprofen, aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, indomethacin (Indocin), ticlopidine (Ticlid), warfarin (Coumadin), and others.

- **Safety Precautions**
  - **Pregnancy and breast-feeding**: Ginkgo is **POSSIBLY UNSAFE** when used during pregnancy. It might cause early labor or extra bleeding during delivery if used near that time. Not enough known.
  - **Children**: Ginkgo leaf extract is **POSSIBLY SAFE**. Some research suggests that a specific combination of ginkgo leaf extract plus American ginseng might be safe in children when used short-term.
  - **Diabetes**: Ginkgo might interfere with the management of diabetes. If you have diabetes, monitor your blood sugar closely.
  - **Seizures**: There is a concern that ginkgo might cause seizures.
  - **Infertility**: Ginkgo use might interfere with fertility
  - **Bleeding disorders**: Ginkgo might make bleeding disorders worse
  - **Surgery**: Ginkgo might slow blood clotting. It might cause extra bleeding during and after surgery. Stop using ginkgo at least 2 weeks before a scheduled surgery
  - http://www.nlm.nih.gov/medlineplus/druginfo/natural/333.html

- **Possible Mechanisms to Reduce Effects of Dementia/AD**
  - Antioxidant [12]
    - Neutralize ROS and iNOS
    - Change micromechanics of erythrocytes
      - Protect mitochondria
      - Improve energy metabolism
  - Anti-inflammatory[12]
    - Inhibit “platelet activating factor”
  - Enhances high-affinity choline uptake [12]
  - Anti-amyloid aggregation effect
    - in vitro study [9]
  - Increase Transthyretin RNA levels in (mouse) hippocampus [10]
    - Transthyretin: beta amyloid transport
  - Possible modulating role of Ginkgo on alpha secretase [10]
    - Secretase: the enzyme that cuts the amyloid precursor protein and prevents fragments from being produced

Convinced?

- 1st Cochrane meta-analysis (Birks et al., 2002; p. 2)
  - 33 randomized trials
  - Ginkgo proved to be more effective than placebo

- More Recent Cochrane (Birks and Evans, 2007; p. 1–2)
  - No significant evidence
  - Inconclusive

Study #1

Ginkgo biloba for mild to moderate dementia in a community setting: a pragmatic, randomized, parallel-group, double-blind, placebo-controlled trial

Rob McCarney, Peter Fisher, Steve Iliffe, Robbert van Haselen, Mark Griffin, Jan van der Meulen and James Warner

- Objectives:
  - The benefit of Ginkgo Biloba as a safe alternative to the Dementia medication that is currently being prescribed.
  - To determine the safety and efficacy of Ginkgo Biloba extract EGb 761 on community dwelling individuals
  - Variables:
    - Independent
      - Cognitive Decline leading to Dementia/AD diagnosis
    - Dependent
      - Intake of Ginkgo Biloba extract EGb 761 or placebo
    - Confounding
      - age, sex and randomization group
    - Other Confounding
      - Diet, exercise habits as youth, occupation (pre-retirement if applicable), medication history, supplement use history, history of head injury… years of education, study site, smoking status, *APOE*E4* status, MCI at baseline, cancer or diabetes in the 5 years before baseline, marital status, body mass index, history of CHD or stroke, self-rated health, depression, upper extremity strength, mobility, activities of daily living

- Methods
  - A 6-week, pragmatic, randomized, parallel-group, double-blind, placebo-controlled trial
  - Dose: 60mg Ginkgo or Placebo twice daily for 6 months
  - Subjects
    - Recruitment:
      - From February 2003 to June 2005
      - Greater London (UK) and surrounding regions
      - Referrals given from general practices, old age psychiatrists, and other healthcare professionals
      - Alzheimer's Newsletters
      - Posters in Age Concern centers

- Sample Size
  - Randomized: n=176
  - Placebo Group: n=88
  - Intervention Group: n=88

- Inclusion Criteria
  - Clinical diagnosis of Dementia from referring clinician
    - subsequently sub-classified using DSM-IV criteria
    - a Mini Mental State Examination (MMSE) score of 12-26
  - 55 years or over
  - Presence of a caregiver
  - Informed consent from their caregiver
  - Sufficient command of English
  - living in the community

- Exclusion Criteria
  - Use of Ginkgo in 2 weeks prior to the baseline assessment
  - Commencement of cholinesterase inhibiting drugs within 2 months of baseline or during follow-up
  - Concomitant warfarin therapy
  - Known bleeding abnormalities

- Intervention
  - Treatment
    - Ginkgo biloba extract EGb 761
  - Placebo
    - Lactose-based pill laced with quinine (to prevent de-blinding)
  - 60 mg twice daily for 6 months
  - Intensive Follow-up group:
    - Randomized at baseline (0)
    - Visits at 0,2,4,and 6 months (endpoint)
      - See Table 1
  - Minimal Follow-up group:
    - Randomized at baseline (0)
    - Visits at 0 and 6 months
  - Interviews were administered at the subject's (or caregiver's) home by trained researcher

- Outcomes Measured
  - Primary
    - Cognitive functioning
      - Measured with ADAS-Cog
      - higher score indicates worse cognition
    - Quality of life
      - rated by the participant and caregiver
      - Measured with QOL-AD
      - higher score indicates better quality of life.
  - Secondary
    - Psychopathology and the resulting distress to the caregiver
      - measured with Neuro-Psychiatric Inventory with caregiver Distress scale (NPI-D)
    - Caregiver-reported daily living and social behavior score
      - measured by the Geriatric Evaluation by Relative's Rating Instrument (GERRI)
      - higher score indicating greater impairment

- Caregiver-reported burden of caring as measures by the 12-item Zarit Burden Interview (ZBI)
  - Higher score indicates greater burden
- Report of caregiver health
  - measured by the visual analogue scale of the European Quality of Life Visual Analogue Scale (EQ-VAS)
  - Higher score indicates better health
- Caregiver-reported global measure of benefit
  - Question at the final follow-up
    - 'If you could continue the medication the person you care for has been receiving in this trial, would you (do you feel that it has helped him/her)?'
    - Answer: yes or no
- Blood coagulation times
  - Measured by Activated Clotting Time (ACT) using near-patient testing with the Coaguchek Pro DM.

- Statistical Analysis
  - Planned *a priori*
  - Documented in analysis protocol
  - Primary analysis was Intention to Treat (IT)
  - ANCOVA was used to compare groups
    - Regression models were used to check analysis
  - Means adjusted in terms of (β)
    - Positive β value favors Ginkgo
    - Negative value favors placebo;
    - 95% Confidence Intervals (CI) and p-values (<0.05)
  - Analysis using all evaluable (i.e. non-imputed) data available at 6 months only
  - Per-protocol analysis
    - Effect of adherence on outcomes

- Results
  - Table 1
    - Flow of study from Baseline to Endpoint
  - Table 2
    - Baseline and Clinical Data
    - Mean Age: 79
    - Total Male: 69 vs. Female: 107
    - Race: Mostly white
    - AD total: 148
    - Vascular Dementia total: 28
    - Mean MMSE score: 22
  - Table 3
    - No significance at 6 months on:
      - ADAS-Cog score
      - participant-rated QOL-AD score
      - carer-rated QOL-AD score
    - More favorable value seen in Placebo group

- Conclusion….
  - No evidence to show EGb 761 at 2 daily doses of 60mg is effective in lessening cognitive decline in subjects with mild dementia.

Table 1. Administration of outcome measures

	Time point in study	Intensive follow-up group		Minimal follow-up group	
		Questionnaire	Subject*	*Questionnaire*	Subject*
Baseline	0	ADAS-Cog, QOL-AD, NPI-D, GERRI	Participant	ADAS-Cog, QOL-AD	Participant
		EQ-5D, ZBI	Carer	EQ-5D, ZBI	Carer
	2 months	ADAS-Cog, QOL-AD, NPI-D	Participant	—	
		EQ-5D, ZBI	Carer		
	4 months	ADAS-Cog, QOL-AD, NPI-D	Participant	—	
		EQ-5D, ZBI	Carer		
End of study	6 months	ADAS-Cog, QOL-AD, NPI-D, GERRI	Participant	ADAS-Cog, QOL-AD, NPI-D, GERRI	Participant
		EQ-5D, ZBI	Carer	EQ-5D, ZBI	Carer

*Subject denotes person assessed by measure. Some assessments are completed by the carer but reporting on the participant (e.g. GERRI and NPI-D). For measures such as this the participant is the subject.

Table 2. Baseline demographic and clinical characteristics of participants, by treatment group

Participants: total sample			
Characteristic	Placebo group ($n=88$)	Ginkgo group ($n=88$)	Total sample ($n=176$)
Mean age[1]	79.7 (7.53)	79.3 (7.77)	79.5 (7.63)
Females, Males[2]	56, 32 (63.6%)	51, 37 (58.0%)	107, 69 (60.8%)
Ethnicity[2]	White: 83 (94.3%) Mixed: 1 (1.1%) Asian: 1 (1.1%) Black: 3 (3.4%)	White: 84 (95.5%) Asian: 2 (2.3%) Black: 2 (2.3%)	White: 167 (94.9%) Mixed: 1 (0.6%) Asian: 3 (1.7%) Black: 5 (3.4%)
Median years of education[3]	10.0 (9.0, 13.1)	10.0 (9.0, 14.0)	10.0 (9.0, 13.3)
Median Indices of Multiple Deprivation score[3]	17.1 (5.9, 44.2)	20.5 (7.3, 40.7)	19.0 (6.3, 43.2)
Number with Alzheimer's disease, vascular dementia diagnosis[2]	76, 12 (86.4%)	72, 16 (81.8%)	148, 28 (84.1%)
Evidence of vascular pathology[2]	44 (50.0%)	42 (47.7%)	86 (48.9%)
Median MMSE score[3]	22.0 (13.0, 25.1)	23.0 (16.9, 26.0)	22.0 (15.0, 26.0)
Mean ADAS-Cog score[1]	25.0 (10.3)	20.4 (8.2)	22.7 (9.6)
Median duration of dementia in years[3]	3.0 (1.0, 8.8)	3.0 (1.2, 7.2)	3.0 (1.0, 8.0)
AChI use[2]	29 (33.0%)	29 (33.0%)	58 (33.0%)
NSAID use[2]	47 (53.4%)	51 (58.0%)	98 (55.7%)
Previous Ginkgo use[2]	8 (10.0%) *Missing* $n=8$	21 (25.0%) *Missing* $n=4$	29 (17.7%) *Missing* $n=12$
Mean participant-rated QoL-AD score[1]	37.2 (6.1) *Missing* $n=3$	36.2 (5.5) *Missing* $n=2$	36.7 (5.8) *Missing* $n=5$
Mean carer-rated QoL-AD score[1]	31.8 (6.4) *Missing* $n=7$	32.1 (6.9) *Missing* $n=8$	32.0 (6.6) *Missing* $n=15$
Median 12-item ZBI score[3]	13.5 (5.9, 25.3)	15.0 (5.0, 27.4) *Missing* $n=3$	14.0 (5.4, 26.6) *Missing* $n=3$
Median EQ-VAS score[3]	80.0 (50.0, 95.0)	77.0 (44.0, 95.0) *Missing* $n=1$	80.0 (50.0, 95.0)

Participants: intensive follow-up group only			
Characteristic	Placebo group ($n=45$)	Ginkgo group ($n=43$)	Total sample ($n=88$)
Median NPI score[3]	9.0 (0.0, 29.2) *Missing* $n=2$	11.0 (0.0, 28.5) *Missing* $n=1$	9.0 (0.0, 28.8)
Mean GERRI total score[1]	2.53 (0.42)	2.58 (0.49)	2.56 (0.45)

Carers			
Characteristic	Placebo group ($n=88$)	Ginkgo group ($n=88$)	Total sample ($n=176$)
Mean age[1]	64.3 (12.9) *Missing* $n=7$	64.0 (14.5) *Missing* $n=4$	64.1 (13.7) *Missing* $n=11$
Females, Males[2]	78, 10 (88.6%)	74, 14 (84.1%)	152, 24 (86.4%)
Number who are the partner of the participant[2]	43 (48.9%)	50 (56.8%)	93 (52.8%)
Number who live-in[2]	57 (64.8%)	58 (65.9%)	115 (65.3%)
Number who are the informal (unpaid) carer[2]	84 (95.5%)	85 (96.6%)	169 (96.0%)

[1]Mean scores are reported with standard deviations.
[2]Numbers reported with percentage of group (e.g. Ginkgo group); or percentage of females or AD sufferers respectively.
[3]Median scores are reported with 10th and 90th percentiles.
[4]In England and Wales, Indices of Multiple Depreivation scores are a way of quantifying the relative poverty of an area and are linked to postcodes (ODPM, 2005).

Table 3. Adjusted difference in means for primary and secondary outcomes

Measure	*N*	Adjusted difference in means (95% CI)[1]	*P*-value
ADAS-Cog[2]	176	−0.823 (−2.701, 1.055)	0.392
Participant-rated QOL-AD[2]	176	−0.187 (−1.542, 1.168)	0.787
Carer-rated QOL-AD[2]	176	−0.981 (−2.551, 0.589)	0.222
NPI[2]	88[3]	−4.512 (−9.176, 0.152)	0.061
NPI-D[2]	88[3]	−2.364 (−5.325, 0.597)	0.121
GERRI[4]	88[3]	−0.119 (−0.241, 0.003)	0.060
ZBI[2]	176	−0.017 (−2.463, 2.429)	0.989
EQ-VAS[2]	176	−1.6715 (−5.922, 2.579)	0.442

[1]Positive values favour Ginkgo.
[2]No significant differences were found in the analyses with evaluable data or in the per-protocol analyses.
[3]Outcome measure administered at baseline in standard follow-up group only.
[4]Significant difference found in the analysis with evaluable data ($n = 75$; $B = 0.142$; 95% CI 0.027, 0.257; $p = 0.016$) and in the per protocol analysis ($n = 51$; $B = 0.156$; 95% CI 0.033, 0.279; $p = 0.014$); in both cases, it indicates a more favourable outcome in the placebo group.

Table 4. MedDRA classification of the adverse events by treatment group

MedDRA category	Placebo group		Ginkgo group	
	Serious	Total	Serious	Total
006 Infections and infestations	1	2	1	2
008 Blood and lymphatic system	0	2	0	1
011 Metabolism and nutrition	1	1	0	2
012 Psychiatric	1	5	1	3
013 Nervous system	0	5	2	5
015 Ear and labyrinth	0	1	0	0
016 Cardiac	1	1	1	1
017 Vascular	0	0	0	1
018 Respiratory, thoracic and mediastinal	1	4	1	1
019 Gastrointestinal	1	5	0	7
020 Hepatobiliary	1	1	0	0
021 Skin and subcutaneous tissue	1	3	0	3
022 Musculoskeletal and connective tissue	0	2	2	3
023 Renal and urinary	0	1	0	0
025 Reproductive system and breast	0	0	0	1
Grand total	8	33	8	30

Study #2

Ginkgo biloba for Preventing Cognitive Decline in Older Adults

A Randomized Trial

Beth E. Snitz, PhD, Ellen S. O'Meara, PhD, Michelle C. Carlson, PhD, Alice M. Arnold, PhD, Diane G. Ives, MPH, Stephen R. Rapp, PhD, Judith Saxton, PhD, Oscar L. Lopez, MD, Leslie O. Dunn, MPH, Kaycee M. Sink, MD, Steven T. DeKosky, MD,

For the Ginkgo Evaluation of Memory

(GEM) Study Investigators

- Objectives for the study
  - Ginkgo has been taken for many years to improve cognitive health, but there are still limited clinical studies which determine the efficacy of the claims linking Ginkgo and neurological protection.
  - To examine whether Ginkgo slows cognitive decline or neurodegenerative diseases in older adults

- Analysis taken from the **Ginkgo Evaluation of Memory (GEM)** study, a randomized, double-blind, placebo-controlled trial; the largest dementia prevention trial documented.

- Variables
  - Dependent: Cognitive Decline according to the Clinical Dementia Rating (CDR) Scale
  - Independent: Intake of Ginkgo Biloba extract EGb 761 or placebo
  - Confounding:
    - age, sex, race, years of education, study site, smoking status, *APOE*E4* status, MCI at baseline, cancer or diabetes in the 5 years before baseline, marital status, body mass index, history of CHD or stroke, self-rated health, depression, upper extremity strength, mobility, activities of daily living and instrumental activities of daily living scores, 3MSE scores, ADASCog scores, CDR sum of boxes, time since randomization, time from the previous visit to the final actual or imputed visit, and reason for censoring
  - Others?
    - Diet, exercise habits as youth, occupation (pre-retirement if applicable), medication history, supplement use history, history of head injury…

- Subjects
  - Recruitment:
    - September 2000 to May 2002
    - from Hagerstown, Maryland; Pittsburgh, Pennsylvania; Sacramento, California; Winston-Salem and Greensboro, North Carolina
  - 7709 screened
    - 4637 Excluded
    - 3072 Randomized
      - 1545 Ginkgo Biloba Group
      - 1524 Placebo Group
  - Inclusion Criteria
    - Mild Cognitive Impairment (MCI) diagnosis at Baseline
    - Clinical Dementia Rating (CDR) global score of 0.5

- Exclusion Criteria:
  - Subjects who score above 0.5 on the CDR Scale (0.5= mild **dementia**) [7]
  - Currently taking warfarin
  - Taking cholinesterase inhibitors for cognitive problems or dementia
  - Unwilling to discontinue over-the-counter *G biloba* for the duration of the study
  - Current treatment with tricyclic antidepressants, antipsychotics, or other medications with significant psychotropic or central cholinergic effects
  - Daily use of more than 400 IU of vitamin E
  - History of bleeding disorders
  - Hospitalization for depression within the last year or electroconvulsive therapy within the last 10 years
  - Diagnosis of Parkinson disease or taking anti-Parkinson medications
  - Abnormal thyroid, serum creatinine, or liver function test results
  - Low baseline vitamin B_{12} levels, hematocrit level, or platelet count
  - Disease-limited life expectancy of less than 5 years
  - Known allergy to *G biloba*.

- Study Intervention
  - 2 daily doses 120 mg Ginkgo Biloba extract (EGb 761) or identical placebo
    - Double-blind, Randomized
  - Neuropsychological Tests given at 6-month visits
    - Modified Mini-Mental State Examination (3MSE)
    - Cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog)
      - After Aug 1, 2004, the ADAS-Cog was given annually in alteration with all-study annual neuropsychological evaluations
  - Diagnostic Neuropsychological Evaluations were administered at anytime throughout the study on an as-needed basis

- Statistical Analysis
  - Each Cognitive Domain underwent 2 tests
    - Scale: Higher values indicate worse performance
    1. Log-transformed for regression models
       - Standardized into *z* scores based on mean and sd at baseline
       - Global score calculated as mean of 5 domain scores
    2. Linear mixed models were used to analyze cognitive decline through the end of follow-up, death, or dementia diagnosis.
       - Adjustments: age at randomization in years, sex, nonwhite race, years of education, MCI, and depression at baseline
  - STATA software used for analysis
  - Tests were 2 sided

- Results
  - Table 1
    - Baseline Characteristics
  - Table 2
    - Cognitive decline is worse with increased time
    - Rates of Cognitive Change
      - No Significant difference between Placebo and Treatment groups
    - No evidence of *G biloba* effecting:
      - global cognitive change
      - specific cognitive domains of memory
      - visual-spatial construction
      - Language
      - Attention
      - psychomotor speed
      - executive functions
    - No differences in treatment effects by age, sex, race, education, *APOE*E4* allele status, or baseline cognitive status (MCI vs normal cognition)

- Table 3
  - Estimated annual rates of change for all individual neuropsychological test scores in their original scales
  - No statistical significance between groups shown between groups when administered various neurological tests
- Conclusion….
  - No evidence to show EGb 761 at 2 daily doses of 120mg is effective in lessening cognitive decline in subjects with mild dementia.

Table 1. Baseline Characteristics of Study Participants by Study Drug Assignment

Characteristics	Study Group: Placebo (n = 1524)	Study Group: *Ginkgo biloba* (n = 1545)	*P* Value[a]
Age, mean (SD), y	79.1 (3.3)	79.1 (3.3)	.88
Male, No. (%)	808 (53)	843 (55)	.39
Nonwhite, No. (%)	76 (5.0)	63 (4.1)	.23
Education, mean (SD), y	14.4 (3.0)	14.3 (3.0)	.12
Depression score, mean (SD)[b]	3.6 (3.4)	3.6 (3.6)	.70
Mild cognitive impairment, No. (%)	226 (14.8)	256 (16.6)	.19
Presence of *APOE**E4* allele, No. (%)[c]	281 (23.0)	297 (24.1)	.52
Modified Mini-Mental State Examination total score, mean (SD)	93.3 (4.7)	93.4 (4.7)	.76
Alzheimer Disease Assessment Scale total score, cognitive subscale, mean (SD)[d]	6.4 (2.7)	6.5 (2.8)	.16
Neuropsychological domains, mean (SD), original scale for each test			
Memory			
CVLT delayed recall (range, 0-16)	8.9 (3.2)	8.7 (3.2)	.04
Rey-Osterrieth Figure Test delayed recall, % retained	72 (19)	71 (21)	.18
Attention			
WAIS-R Digit Span, forward (range, 2-14)	7.8 (2.1)	7.7 (2.1)	.17
Trail Making Test Part A, seconds to complete (sample range, 17-240)[d]	43.3 (15.8)	44.4 (16.1)	.06
Visuospatial abilities			
Rey-Osterrieth Figure Test copy (range, 0-24)	22.1 (2.4)	22.0 (2.4)	.61
WAIS-R Block Design (range, 0-24)	12.0 (4.4)	11.5 (4.3)	.007
Language			
Animal fluency, No. of words generated in 60 seconds	15.8 (4.3)	16.0 (4.4)	.35
Boston Naming Test (range, 0-30)	26.6 (2.9)	26.6 (3.0)	.89
Executive functions			
Trail Making Test Part B, seconds to complete (sample range, 16-240)[d]	107 (39)	107 (39)	.95
Stroop Color/Word Test interference (sample range, 3-157)	77.0 (21.8)	75.0 (22.7)	.02

Abbreviations: CVLT, California Verbal Learning Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised.
[a] *P* values were computed using χ^2 (discrete variables) or *t* test (continuous variables).
[b] Centers for Epidemiologic Studies Depression total score; 30-point scale.
[c] *APOE* genotype data were available for 2452 participants.
[d] Higher score indicates worse performance.

Table 2. Results of Linear Mixed Models for Each Cognitive Domain and Global Cognition[a]

	Treatment (*G biloba*) Effect: Overall Difference in *z* Scores vs Placebo, Mean (95% CI)	Annual Rate of Change in *z* Scores, Mean (95% CI)		Treatment × Time Interaction: Annual Difference in Rates of Change Between *G biloba* and Placebo, Mean (95% CI)
		Placebo	*G biloba*	
Memory	0.034 (–0.019 to 0.086)	0.041 (0.032 to 0.050)	0.043 (0.034 to 0.051)	0.002 (–0.010 to 0.013)
P value	.21	<.001	<.001	.79
Attention	0.037 (–0.012 to 0.086)	0.048 (0.041 to 0.054)	0.043 (0.037 to 0.050)	–0.004 (–0.013 to 0.005)
P value	.14	<.001	<.001	.37
Visuospatial abilities	0.038 (–0.017 to 0.093)	0.118 (0.108 to 0.128)	0.107 (0.097 to 0.117)	–0.011 (–0.022 to 0.001)
P value	.17	<.001	<.001	.08
Language	–0.041 (–0.093 to 0.011)	0.041 (0.033 to 0.048)	0.045 (0.037 to 0.054)	0.005 (–0.005 to 0.014)
P value	.13	<.001	<.001	.33
Executive functions	0.013 (–0.042 to 0.069)	0.089 (0.082 to 0.096)	0.092 (0.086 to 0.099)	0.003 (–0.006 to 0.013)
P value	.64	<.001	<.001	.49
Global cognition	0.015 (–0.018 to 0.047)	0.071 (0.065 to 0.076)	0.069 (0.064 to 0.074)	–0.002 (–0.009 to 0.005)
P value	.38	<.001	<.001	.65

Abbreviations: CI, confidence interval; *G biloba*, *Ginkgo biloba*.

[a] Higher coefficients indicate worse test performance. Adjusted for age, sex, nonwhite race, years of education, mild cognitive impairment, and depression score at baseline. Scores are derived from the mean of 2 tests for each cognitive domain, with global cognition representing the mean of the 5 cognitive domain scores. (See Table 3 for estimated annual rates of change for each individual test.) As described in the Methods, test scores were transformed so that higher scores were worse and skewed measures were log-transformed. Scores were then standardized into *z* scores. Annual rates of change in each cognitive domain are presented. Results of the other components of the model are shown in the eTable.

Table 3. Annual Rates of Change for Individual Neuropsychological Test Scores by Study Drug Assignment[a]

Neuropsychological Domain/Test	Annual Rate of Change in Original Scores, Mean (95% CI)		*P* Value[b]
	Placebo	*Ginkgo biloba*	
Memory			
CVLT delayed recall (range, 0-16)	−0.15 (−0.18 to −0.12)	−0.14 (−0.17 to −0.11)	.71
P value	<.001	<.001	
Rey-Osterrieth Figure Test delayed recall, % retained	−0.002 (−0.004 to 0.0003)	−0.004 (−0.006 to −0.002)	.14
P value	.09	<.001	
Attention			
WAIS-R Digit Span forward (range, 0-14)	−0.03 (−0.04 to −0.01)	−0.02 (−0.04 to −0.01)	.68
P value	<.001	.006	
Trail Making Test Part A, seconds to complete (range, 12-240)[c]	1.55 (1.34 to 1.77)	1.45 (1.23 to 1.66)	.50
P value	<.001	<.001	
Visuospatial abilities			
Rey-Osterrieth Figure Test copy (range, 0-24)	−0.41 (−0.44 to −0.38)	−0.38 (−0.41 to −0.35)	.28
P value	<.001	<.001	
WAIS-R Block Design (range, 0-24)	−0.19 (−0.22 to −0.15)	−0.14 (−0.17 to −0.11)	.06
P value	<.001	<.001	
Language			
Animal fluency, No. of words generated in 60 seconds	−0.22 (−0.26 to −0.19)	−0.26 (−0.30 to −0.22)	.17
P value	<.001	<.001	
Boston Naming Test (range, 0-30)	−0.04 (−0.07 to −0.02)	−0.06 (−0.08 to −0.04)	.31
P value	<.001	<.001	
Executive functions			
Trail Making Test Part B, seconds to complete (range, 16-240)[c]	3.27 (2.90 to 3.64)	3.47 (3.10 to 3.84)	.44
P value	<.001	<.001	
Stroop Color/Word Test interference (range, 0-161)	−2.08 (−2.26 to −1.90)	−2.04 (−2.21 to −1.86)	.75
P value	<.001	<.001	

Abbreviations: CI, confidence interval; CVLT, California Verbal Learning Test; WAIS-R, Wechsler Adult Intelligence Scale–Revised.
[a] These values were transformed as described in the "Methods" section of the text and in Table 2 to derive the *z* scores used to compare cognitive domains.
[b] *P* values from treatment-by-time interaction term: average annual difference in rates of change between *G. biloba* and placebo groups.
[c] Higher values (times to completion of task) indicate worse test performance.

Case Study

- Douglass is a 45 year old taxi driver.
- Experiencing what he described to be “age-related forgetfulness”, but his wife is becoming more concerned with his worsening memory and frequent word finding problems. After he got lost on a familiar route, his wife was able to convince him to see his doctor.
- After completing a full examination, the doctor concludes that Douglass has Type 3 early-onset familial Alzheimer’s Disease.
- The doctor has some concerns about his diet history and inactive lifestyle behaviors and refers him to see a Dietitian.

- Height: 6’0”
- Weight: 68kg
- BMI: 20.3
- Physical activity
  - Sitting in taxi for 8 hour per day/ 5 days per week
  - Weekend activities: watching television, working on cars
- Diet History
  - 24-hour Recall

  Breakfast
  - Coffee with half and half

  Lunch
  - ½ Turkey sandwich on wheat bread

  Dinner (ate a few bites of each before getting distracted)
  - ½ c rice
  - ½ c mixed vegetables
  - 3oz steak

Remember….

- Nutrition Goals for Dementia
  - Maintain a reasonable weight (BMI 22-27)
  - Provide sufficient kcals
  - Minimize confusion in the environment:
    - one food at a time, simple place settings, plate should be a different color than the table, add condiments prior to serving
  - Provide alternate opportunities to eat if the patient has difficulty sitting still
    - (ie. Snacks, finger foods)
  - Maximize food intake during lunch
    - Cognition is usually best [1]

- Emphasize foods high in antioxidant:
  - Fruits, Vegetables, Whole grains
- Try to implement daily exercise at least 30 minutes per day

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