Dementia Prevention
A Call to Action

Cook Library
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A man in video store stares at a shelf labeled, “Videos You’ve Forgotten You’ve Seen Already.”
Goals – 2017 update

- Scope of Dementia
- Pathology of Alzheimers
- Modifiable Risk factors for Dementia
- Preventive Activity/lifestyle effects
- Specific promising nutrients, foods and diets
- Horizon
Cognition

- Memory
- Executive Function
- Visuo-spatial perception
- Language
- Attention
Alzheimer’s Disease (AD)

- Progressive dementia of insidious onset
- Accelerated death of cerebral neurons
- Early and late onset
- Amyloid plaque outside brain cells
- Neurofibrillary tangles inside brain cells
- Cholinergic transmission
- Mitochondrial energy production
Alzheimer’s Dementia and Vascular disease OVERLAP

- Estimate 1/3 AD cases worldwide attributable to modifiable risk factors—Diabetes, midlife HTN, physical inactivity

- 1/3 of >85 yo without dementia have pathology consistent with dementia

- At autopsy 40% of AD also have severe vascular pathology
Scope of Dementia

- 2011  4.5 million in US > 65 yo with AD
- by 2050  13.8 million  130 million worldwide
- Rural India 1.1%

• UpToDate 2016
Scope of Dementia

- >1% of ages 60–64
- >16–30% greater than 85 years
- >8 million Americans mild cognitive impairment

- UpToDate 2016
Family History of Alzheimer’s disease

- Strongest association with first degree relatives
- 2–3 fold increase in risk
- Higher with additional relatives
- 20 different genes a role in 80% of AD

- 40% of people with AD have ApoE4 gene
- If from each parent risk increased 4X
  - *Mind Mood Memory MGH 2016*
Value of testing ApoE4?

- MGH *Mind Mood Memory* “only research basis”
  
  But,
  
  - Testing may decrease anxiety and improve health behaviors

  - Christensen KD *Annals Int Med* 2016
Down’s Syndrome

- Virtually all by age 40 have neurofibrillary tangles and amyloid deposition to meet criteria of AD
- 10 year delay between pathologic changes in the brain and clinical diagnosis of dementia
- Also increased inflammatory gene expression

Head E Eur J Degen Dis 2014
Some common non-genetic Risk Factors

- Brain trauma with loss of consciousness > 30 min
- 2nd hand smoke (China 2.4X)
- Air pollution
- Insecticides
- Gender – women live longer
- Less formal education
- “Western” diet

- UptoDate 2016
48% Dementia cases attributable to modifiable risk factors

- Smoking
- Midlife obesity
- Physical inactivity
- Diabetes
- Hypertension
- Major depression
- Low education attainment
How is Alzheimer’s treated medically (i.e. Drugs)?

- **Mild to moderate:**
  - cholinesterase inhibitors (donezipil/ aricept)

- **Moderate to severe:**
  - Glutamate production (memantine/ Namenda)
    - (moderate–severe disease)

- BOTH: help symptoms over the short term, but do not modify disease trajectory
Why Prevention?

Yellow Emperor Internal Medicine
2697–2598 BCE

“Suppressing chaos once it arises in the body is like digging a well after becoming thirsty or forging weapons after going into battle.”
Why Prevention?

- NIH spends $1.3 billion/year on dementia research (0.8% of what dementia will cost Medicare and Medicaid in 2015, $154 billion)

- Delaying dementia onset 5 years, by 2050 would reduce incidence 50% and cost by 1/3rd

  - NY Times April 23, 2015
Processes to target via prevention

- Address modifiable risk factors - vascular risk
- Blood vessel disease (atherosclerosis)
- Oxidative stress
- Excessive inflammatory response
- Beta amyloid accumulation
Potentially Modifiable Risk Factors

- Midlife hypertension (high blood pressure) meds decrease dementia 20–55%
- Midlife obesity (9100 men abdominal fat 23 yrs 50% increase in stroke)
- Physical inactivity
- Cognitive inactivity/ low educational attainment
- Smoking—damages blood vessels
- Depression

Larsen B *Annals Int Med* 2011
Potentially Modifiable Risk Factors Continued

- Psychosocial and mid-life work stress
- Social isolation
- Low thyroid function
  - B12, folate deficiency
- Vitamin D, E deficiencies
- Adverse effects of medications for sleep, anxiety, and pain
Meds that can affect cognition

- Benzodiazepines
  - Diazepam (Valium)
  - Alprazolam (Xanax), lorazepam (Ativan)
- Anticholinergics,
  - Benadryl, Elavil, Sinequan
- Barbiturates other sedative–hypnotics
- Captopril (Capoten)
- Cimetidine (Tagamet)
- Paroxetine (Paxil)
- Oxybutinin (Ditropan)
Statins decrease Alzheimer’s Risk

- Hispanic men 29% decrease
- black women 18%
- white women 14%
- white men 11%
  but they did not decrease the risk of Alzheimer’s among black men

Zissimopoulos JAMA Neurol. 2016 Dec 12.
Statins **DO NOT** decrease Alzheimer’s Risk *2017*

- 2 large RCTs 25000 did not show protective effect on cognition

McGuiness B, Cochrane Database 2016

UpToDate August 2017
British Medical Journal 2017

- 2017
- 13,000 Nurse’s health study, proton pump inhibitor antacids NO increased dementia.
“Still, a brisk walk can be just as effective.”
Physical activity THE CRUCIAL INTERVENTION

- 12 studies all 2–6 months
- Limited evidence 3–4X week > 30 min brisk activity
Physical activity THE CRUCIAL INTERVENTION

STUDY 1:
- 16 prospective studies demonstrate that regular physical activity (approx 30–60 minutes/day 3 days/week of brisk walking)
- 28% decrease in overall dementia
- 45% decrease in AD

STUDY 2:
- 900 regularly active participants > 65yo
- Brain scans– less gray matter and hippocampal atrophy

- UpToDate 2016
Physical activity THE CRUCIAL INTERVENTION?

- British Medical Journal prospective exercise ages 35–55, 28 years of follow-up failed to show protective effect

  • UpToDate 2016
Multiple Interventions Study

- 2 years controlled, prospective trial = gold standard!
  - 60–75 yo,
  - Diet
  - Exercise
  - Cognitive training
  - Reduced vascular risk factors

- Clear benefit shown  (7% treated group back pain!)
- Ngandu T Lancet June 2015
Cognitive Training Study

- Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Study

- 2,832
- ten 60–75 minute sessions over 5–6 weeks
- Memory training
- Reasoning training.
- delay onset of functional decline in Independent ADLs

Complex work

- 10,079 members Swedish twin registry
- Complex work, especially with other people, reduced the incidence of Alzheimer’s

- occupational complexity scores—working with data, things and people

Mind–Body Studies

Reading, playing board games, playing musical instruments, dancing all reduce risk of dementia

Vergese J NEJM June 2003

Crossword puzzle participation at baseline delayed onset of accelerated memory decline by 2.54 years.

Pillai JA J Int Neuropsychol Soc. 2011

3675 French board game players over 5 yrs 15 % fewer dementia, less depression

Dartiques J BMJ 2014

Commercial “brain training”– limited effect to rehearsed tasks

UTD 2017
Co-factors for cognition

- Social activity
- Sleep
- Mental activity
- New language fluency
- Hearing aids 2017 *
- Corrected vision
Hearing loss and Dementia?

- Loss of associated neural pathways, atrophy?
- 666 community dwelling elderly with hearing loss—hearing aids no effect on cognitive decline
  
  - Dawes P Int J Audiol 2015
Controversy

- NIH Roundtable 2011
  - (Daviglus M. L. Arch. Neurol. 2011)
    - “No definitive evidence for benefit of any preventive strategy…..deserve further study and exploration”
    - “Marginalized, patronized epidemiologic and animal dementia researchers” as demonstrating “poor scientific quality”

- Push back– far from consensus
  - Swaminathan A Front Aging Neurosci. 2014
Hippocrates
460–377 BCE

“Let medicine be our food and food be our medicine”
Good nutritional science is difficult

1. Complex, studies–single compounds

2. Prospective studies of combined nutrients and behavior interventions at their “INFANCY”

3. “Western” diet might interfere with benefit studied

4. Omega 3 benefit undermined by omega 6’s.

5. AD can take 10–20 years to develop

Swaminathan A Front Aging Neurosci. 2014
Alzheimer's disease

- Aging
- Amyloid deposition
- Vascular compromise
- Neuronal injury and loss
- Compromised metabolism
- Neurofibrillary degeneration
- Synaptic loss
- Inflammation

Supporting factors:
- Trace minerals
- Antioxidants
- Plant flavonoids
- Metabolic substrates
- Vitamins
- Omega-3 fatty acids
“If we can steer people into eating a healthier antioxidant rich–diet, we could forestall the onset of Alzheimer’s by five or ten years. That’s a big thing.”

James A. Joseph PhD
Assoc. Prof of Tuft’s Friedman School of Nutrition   2005
Factors contributing to poor nutrition

- Poverty
- Isolation
- Depression
- Dementia
- Bereavement
- Alcoholism
- Contemporary food system
- Time-poverty
Virgin press olive oil.....antiinflammatory
Tomato sauce..........lycopene–antioxidant
Red wine/ grapes..........resveratrol
Garlic, onions, oregano, anchovies
Fruits, vegetables, whole grains, seeds, nuts, mod fish and poultry, not excessive beef, sat fat, sugary drinks
Mediterranean diet—Blood vessel health

low in sugars, moderate in protein and high in fresh fruits and vegetables, along with healthy fats.

- no single "Mediterranean diet." At least 16 countries border the Mediterranean Sea.
- Hallmark, minimally processed foods. The emphasis on **fresh** vegetables alone makes it far healthier than the standard American diet, which is very high in processed foods.
Olive oil stabilizes tau protein
3 Diets decrease risk of AD

- Mediterranean diet 18 studies, 5 RCTs
- Dietary Approaches to Stop Hypertension (DASH) diet
- A hybrid diet the Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND)
  - 4 berry servings/wk
  - 2 vegetable servings/day
  - Fish once a week

Swaminathan A *Front Aging Neurosci.* 2014
Foliage

• 579 >60 yo, over 14 years 57 developed Alzheimer’s

• Those with recommended daily amount of folate (1mg) reduced risk by 55%

Corrada M, Alzheimer’s and Dementia 2005
B Vitamins

- Folate more easily absorbed from supplement form

- Needs other B-vitamins to help
  - B1, B2, B6, B12

- 5–20% of us have a sluggish form of the enzyme to use folate–MTHFR gene

- **BUT** Up–To–Date 2017 * 22,000 11 RCTs, B vitamins NO IMPACT on cognition
Beta Carotene

- Physicians’ Health study (extension) 4000
- Clear benefit on cognition 2012

- carrots
- Sweet potatoes
- Kale, spinach
- Winter squash
- Apricots, cantoloupe
Vitamin E Reduces Oxidative Stress

- Up-to-Date recommends Vitamin E 400–800 IU for anyone with strong family history of Alzheimer’s

  Christen Y Am J Clin Nutr 2000; 71:621S

  Rotterdam Study Vit E and C 2012
VITAMIN E Reduces Risk of AD

- 17 studies
- AD patients lower Vitamin E levels

(Vit E supp > 400 IU/d 2005 controversy, increase heart disease 1/256)
Vitamin E foods

- Wheat germ
- Sunflower/ safflower oils
- Sunflower seeds
- Leafy green vegetables
- Asparagus
- Peanuts
- Almonds
- Sweet peppers
Antioxidant nutrients

- Clove, allspice, cinnamon, saffron, bayberry leaf, nutmeg, dill, oregano, sage, peppermint leaves, thyme, dark chocolate, green and black tea, berries, pomegranate

- **Garam masala** lab, animal studies MGH newsletter
  - Cinnamon
  - Nutmeg
  - Cloves
Antioxidant nutrients

- Selenium—brazil nuts, saffron, scallops, cereals, grains, fish, meat
- Unsweetened cocoa powder greatest benefit
- dark chocolate with at least 72% cocoa solids.

Cleveland Clinic *Healthy Brains*
Nutrition

“Well, so much for antioxidants.”
Anti-inflammatory nutrients

- Seafood, ground flaxseed omega 3’s
- Turmeric, –yellow, Indian food, curries, mustards
- Quercetin–capers, onions, apples, spinach, tea, broccoli, pears, raspberries, blackberries
- Capsaicin–hot peppers
- Oregano
- Dark chocolate flavanoids increase aterial flow
Seafood

- omega 3– rich fish
- 815 people aged 65–94 those who ate fish once or more per week had 40% the dementia incidence of those who rarely or never ate fish

Morris MC Arch Neurol 2003;60:940
Omega 3 Fatty Acids

- DHA 900 mg/d in elderly with cognitive decline for 24 weeks
- 7 years age difference in dementia– memory, visuo–spatial learning

Yurko-Mauro K. *Alzheimers Dement.* 2010
Well tolerated, safe, potential major benefit
Large European study fish oil supplement benefit only if normal cognition
Another large study benefit only if ApoE4 gene negative (60% of AD patients are ApoE4 negative)
Confounders–ApoE4, omega 6 intake

- Swaminathan A *Front Aging Neurosci*. 2014
Omega 3 Fatty Acids?

- 2017 * 4205 elderly No effect on cognition in 5 years
- ApoE4 carriers may benefit

- UpToDate 2017
“And what reared its ugly head today?”
Toxins in fish

- Mercury– swordfish, tilefish, king mackerel, Chilean sea bass, some canned tuna
- Health conscious “overconsumers” of fish San Francisco 123 private IM practice 10X national Hg levels

Safest fish nutrients

- Lower in food chain—sardines, anchovies
- Non-farmed
- Not fresh water
- Avoid excess cod liver oil—Vitamin A psychosis
- Good Manufacturing Practices (GMP)
  Extraction procedure for omega 3’s—removes metal and PCB toxins

- krill
Choline – neurotransmitter building block

- Liver
- Meats
- Fish
- Nuts
- Beans
- Peas
- Eggs
- spinach
Vitamin D

- Vitamin D requires sunlight on the skin unless supplemented
- Mixed results of Vitamin D levels and dementia
- 1658 elderly followed 5.6 years, deficient 25 hydroxy Vitamin D levels was assoc with 2X risk of AD
  Littlejohns TJ Neurology. 2014
- Executive function benefit, not memory
  - Landel V J Alz Dis 2013
Vitamin D

- 2000 IU/d supplement

Sardines
Salmon
Tuna
Shrimp

Butter,
Sunflower Seeds
Liver
Cereal
Egg yolk,
fortified milk
A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease

- Mild–moderate AD
- Up to 1 gram twice/day
- Improved blood and CSF biomarkers

• Turner RS *Neurology* Sept 2015
Other nutrients and Risk for AD

- Mixed results—Mitochondrial support CoQ10–
- Ongoing PreADViSe (Vit E and selenium) trial—largest prospective preventive trial
- Not in scientific reports—Medium Chain Triglycerides—coconut oil
- Early, small studies—Axona
- Early, small studies—Souvenaid

- Swaminathan A Front Aging Neurosci. 2014
Antioxidant supplements—future?

- L-Acetyl-carnitine  NOT D- form muscle wasting
- Alpha-lipoic acid
- N-acetyl cysteine (NAC)
- CoQ10
- ProceraAVH  (Acetyl-carnitine, Vinpocitine, Huperzine)
  1.4 million $ to FTC “reverse age associated memory loss” “like eyeglasses for the eyes”
- Pravagen— No human data published
Antioxidant supplements—future?

- Huperzine A inhibits enzyme so more acetylcholine transmission between nerve endings lasts 3 hours, more effective than meds

- Commercial forms: *Alpha Brain, Extension IQ, Memorall, Memory Mate*
  - UpToDate 2017
Horizon 2017 *

- Stress reduction – role of meditation 6 pilot studies
- Non-invasive brain stimulation – multiple
- Immunomodulators
- – targeted drugs
- Vaccines – markedly reduced fibrillary tangles but adverse effects stopped trial
- Combined diet, exercise, cognitive retraining
Why Prevention?

- NIH spends $1.3 billion/year on dementia research (0.8% of what dementia will cost Medicare and Medicaid in 2015, $154 billion)

- Delaying dementia onset 5 years, by 2050 would reduce incidence 50% and cost by 1/3rd

  - NY Times April 23, 2015
Target vascular risk factors

- Smoking
- Hypertension less than 140/90 ok goal
- Physical inactivity
- Midlife obesity
- Diabetes

Also

- Midlife work stress
- Major depression
AVOID

- “Western” diet of sat fat, refined carbs
- Pollution
- Head injury
- Excessive alcohol
Bottom line

- Moderate exercise **CRUCIAL INTERVENTION**
- 30–90 minutes of brisk activity 3 times a week
Bottom line

- Mediterranean diet–DASH/ MIND 2017 *

Diet:

Whole foods, rainbow of fruits, vegetables, seeds, nuts, culinary herbs and spices, virgin first press olive oil, fish, poultry, limited red meat
Vitamins E, D and probably C
Omega 3 fish oil supplement
Mixed B –12, folate, B6 vitamin
Culinary herbs and spices
“In science there are many beautiful ideas slain by ugly facts.”

Thomas Huxley

An open mind and healthy skepticism are good traveling companions.

Anonymous
Resources

- Mass Gen Hosp  *Mind Mood and Memory* newsletter
- *Improving Memory* 2015 Harvard Medical School Special Health Report
- Brain Health Guide– free Cleveland Clinic
Resources

- The Brain Book: Development, Function, Disorder, Health
  by Dr. Ken Ashwell and Richard Restak

- National Geographic Complete Guide to Brain Health: How to Stay Sharp, Improve Memory, and Boost Creativity
  by Michael S. Sweeney
Resources

- Power Foods for the Brain: An Effective 3-Step Plan to Protect Your Mind and Strengthen Your Memory by Neal D. Barnard, MD

- The SharpBrains Guide to Brain Fitness: How to Optimize Brain Health and Performance at Any Age, by Alvaro Fernandez

- Grain Brain by David Perlmutter MD
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