Evidenced-Based Approaches for Promoting Brain Health and Preventing AD

Mercedes M. Rodriguez-Suarez, MD, FAPA
Psychiatrist/Geriatric Psychiatrist Miami VAMC
Assistant Professor of Psychiatry
University of Miami
Miller School of Medicine, Miami, Florida
Disclosure

- Nothing to disclose
Objectives

- Definition of Brain Aging
- Definition of Healthy Brain Aging
- Discuss Potential Modifiable Risk Factors for AD and related dementias and review the evidence to prevent AD by controlling risk factors
- Discuss the Role of Lifestyle Changes in decreasing the risk of dementia and improving the quality of health and longevity
- Conclusions
Brain Aging

• Characteristics of brain aging is loss of brain volume (white matter > gray matter) especially in the hippocampus and frontal lobes; loss of myelin; synapses and the dendritic arbor; cytoskeletal changes (accumulation of neurofibrillary tangles and deposition of amyloids in brain and blood vessels). Infarcts of various sizes and other evidence of cerebrovascular disease.

• Aging is associated with progressive losses in function across multiple systems (sensation, cognition, memory, motor control and affect) and they occur with increasing age.
Healthy Brain Aging

- Maintenance or improvement of cognitive performance
- Larger brain and hippocampal volumes were associated with preserved cognitive function
- Ability to make decisions and remain independent
- Avoidance of disease and disability by maintenance of physical, cognitive and sustained social engagement

Example of Healthy Brain Aging

Madame Jeanne Calment 1875-1997

Lived 122 years!

Guinness Book of Records as the “Oldest person Ever”

What was her secret????
Road to Healthy Brain Aging:

- Preserve cognition (identify modifiable risk factors for AD)
- Improve physical function (identify modifiable risk factors and make lifestyle changes)
- Improve social engagements
- Reduce Stress and reduce risk factors
- Erickson: “Integrity versus Despair”
  - Integrity = wisdom
  - Despair = time running out
    - fear of death
Barriers to Healthy Aging

Modifiable Risk Factors
- Unhealthy Diet
- Physical Inactivity
- Tobacco Use
- Alcohol Use
- Drug use
- Polypharmacy
- Stress/Sleep

Intermediate Risk factors
- Raised blood pressure
- Raised Blood glucose
- Abnormal lipids
- Over weight /obesity
- Heart disease
- Pulmonary disease
- Mental Illness
- Arthritis
- Osteoporosis
- Dental care
Non-Modifiable Risk Factors

- Age
- Family History
- Genetic Factors
  - For AD Early onset AD mutations: Presenilin-1 (30-70%); APP (10-15%); Presenilin-2 (<5%)
  - Late Onset AD: APOE-4
Alzheimer’s Disease

• 5.3 million Americans have AD (Alzheimer’s Association 2009). By 2021 the number is expected to increase to 7.5-9 million and by 2051 it could reach 12.6-16 million

• It accounts for 66% of dementias in older adults

• 33-50% of people aged 85 and older have AD

• Women account for 66% of cases

• AD currently cost $100/year and could cost $300 billion/year within 30 years

• AD develops over decades and dementia can affect a person over 3-20 years
Dementia and AD: importance of life-long exposure to multiple factors

<table>
<thead>
<tr>
<th>Birth</th>
<th>Childhood-2nd decade</th>
<th>Adult life-Middle age</th>
<th>Transition</th>
<th>Old age</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>60</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Healthy brain  

Genetic  

Environment  

Alzheimer brain

Mangialasche, Kivipelto et al., 2012
Probable Modifiable Risk factors for Alzheimer’s disease

- Hypertension
- Diabetes mellitus
- Hyperlipidemia
- Smoking
- Alcohol
- Head Trauma
- Depression
- Elevated Homocysteine
Dementia in advanced age

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

Viswanathan, et al., Neurology 2009
Neurovascular Coupling in the Normal Brain and in Hypertension, Stroke and Alzheimer’s disease

- Regulation of cerebral blood flow (CBF) involves coordinated interaction of neurons, glia, and vascular cells

- Neurons & glia generate signals → vascular change → increased CBF

- Pathological conditions such as AD, hypertension, ischemic stroke disrupt neurovascular coupling → CBF not matched to metabolic needs

- Cerebrovascular dysregulation mediated by the enzyme, NADPH oxidase, a major source of cerebral vascular free radicals

Ref: Girouard H, Iadecola C. J Appl Physiol, 2006; 100:328-335
Diabetes – A Strong Risk Factor for Cognitive Dysfunction and Alzheimer’s disease (AD)

- Type I and Type II diabetes can lead to heart disease, stroke, renal failure, cognitive dysfunction and AD.
- Duration of diabetes, especially, is an important risk factor for AD.
- Hyperinsulinemia and hyperglycemia preceding overt diabetes also increase the 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.
Diabetes

- Insulin resistance and hyperinsulinemia both alter insulin signaling in the brain – this may contribute to the impact of type II diabetes on cognition and development of AD.

- Using transgenic mouse model of AD → diabetes can accelerate AD – associated changes in the brain.

Ref: Dr. Pamela Maher, The Salk Institute
Serum Lipids are Related to Alzheimer’s Pathology in Nursing Home Residents\(^{(1)}\)

- A study at the Jewish Home & Hospital in NYC by Leslie Libow, MD and his group
- For 358 nursing home residents, serum lipids were determined at admission and neuropathologic diagnoses were established at autopsy
- Residents with any AD pathology vs. those without AD pathology had higher mean serum total cholesterol \((p=0.02)\) and higher mean low-density lipoprotein \((p=0.03)\)

Cigarette Smoking is a Risk Factor for Alzheimer’s Disease: An analysis Controlling for Tobacco Industry Affiliation

- Cataldo and colleagues at UCSF reviewed 43 published studies from 1984-2007
- Author’s of ¼ of studies had tobacco industry affiliation
- Average risk of a smoker developing AD
  - studies without tobacco industry affiliation = 1.72
  - studies with author/s having an affiliation = .86

Ref: Cataldo JK, et al. Journal of Alzheimer’s Disease, Online, Jan 2010
Moderate Alcohol Intake is Associated with Lower Dementia Incidence: Results from the Ginkgo Evaluation of Memory Study (GEMS)

- 3,069 community dwelling adults aged 75 or above without dementia in the GEMS study were followed for 6 years
  - 2,587 were cognitively normal at beginning of study
  - 482 had MCI
- Goal: To determine the relationship between alcohol intake and incident dementia
  - intake determined by self-reports as –
    - light = 1-7 drinks/week
    - moderate = 8-14 drinks/week
    - heavy = > 14 drinks/week
Moderate alcohol intake (1-2 drinks/day) associated with a 37% lower risk of dementia in participants with normal cognition at baseline, but not in MCI patients.

For those with MCI at baseline:
- any alcohol intake was associated with a faster rate of cognitive decline
- heavy drinkers (> 14 drinks/week) were nearly twice as likely to develop dementia compared to non-drinkers with MCI

Those results support current recommendations to not exceed one drink/day for women and 2/day for men.

Ref: Sink KM, et al. ICAD, July 2009
Amyloid Precursor Protein (APP) Secretases as Therapeutic Targets in Traumatic Brain Injury (TBI)

- A-Beta peptides accumulate rapidly after TBI in animals and humans
- In mouse models, blocking Beta or Gamma secretase ameliorates cognitive and motor deficits and decreases cell loss
- Secretase inhibitors may be useful in TBI

Change in Depression Symptoms During the Prodromal Phase of Alzheimer’s Disease

- Rush Religious Orders Study followed 917 older Catholic clergy for 13 years – 190 developed AD
- Having more depressive symptoms at baseline was associated with increased incidence of AD and MCI

Plasma Homocysteine as Risk Factor for Dementia and AD

- Prospective study of 1092 subjects (667 female; 425 male), mean age 76 from the Framingham Study were followed for 8 years
- 111 patients developed dementia (83 AD)
- Plasma homocysteine level of 14 micromol per liter or greater resulted in a near doubling of risk for AD

- Seshadri S, et al. NEJM, Feb 2002;346 (7)466-68
AD IS A MULTIFACTORIAL DISEASE

APOE, Other genes

RISK FACTORS
- Alcohol misuse
- Hypertension
- Obesity
- Dyslipidemia
- Diabetes
- Vascular insults
- Neuronal damage

PROTECTIVE FACTORS
- Physical activity
- Cognitive and social activity
- Education

Brain reserve

Mangialasche, Kivipelto et al., 2012
PREVENTION OF COGNITIVE IMPAIRMENT AND AD

- HOW AND WHEN???
## Midlife risk profile, 20 years prediction

<table>
<thead>
<tr>
<th>CAIDE Dementia Risk Score</th>
<th></th>
<th>Score 16%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>&lt; 47</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>47-53</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;53</td>
<td>4</td>
</tr>
<tr>
<td>Education, years</td>
<td>≥10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>7-9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0-6</td>
<td>3</td>
</tr>
<tr>
<td>Sex</td>
<td>Women</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>≤140</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 140</td>
<td>2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>≤30</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>2</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>≤6.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 6.5</td>
<td>2</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Active</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Inactive</td>
<td>1</td>
</tr>
</tbody>
</table>

Kivipelto et al., Lancet Neurology 2006
# Midlife risk profile, 20 years prediction

<table>
<thead>
<tr>
<th>CAIDE Dementia Risk Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 47</td>
<td>0</td>
</tr>
<tr>
<td>47-53</td>
<td>3</td>
</tr>
<tr>
<td>&gt;53</td>
<td>4</td>
</tr>
<tr>
<td><strong>Education, years</strong></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>0</td>
</tr>
<tr>
<td>7-9</td>
<td>2</td>
</tr>
<tr>
<td>0-6</td>
<td>3</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0</td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
</tr>
<tr>
<td><strong>Systolic BP, mmHg</strong></td>
<td></td>
</tr>
<tr>
<td>≤140</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 140</td>
<td>2</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>2</td>
</tr>
<tr>
<td><strong>Cholesterol, mmol/l</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 6.5</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 6.5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>0</td>
</tr>
<tr>
<td>Inactive</td>
<td>1</td>
</tr>
</tbody>
</table>

**SCORE** 7%

Kivipelto et al., Lancet Neurology 2006
CAIDE Dementia Risk Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Category 1</th>
<th>Category 2</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>&lt; 47</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>47-53</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt; 53</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Education, years</td>
<td>≥ 10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>7-9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0-6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sex</td>
<td>Women</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>≤ 140</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 140</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>≤ 30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 30</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>≤ 6.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 6.5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Active</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Inactive</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

SCORE = 2%

Kivipelto et al., Lancet Neurology 2006
The Role of Lifestyle changes to Prevent AD and Promote Healthy Brain Aging

- Nutrition/Diet
- Physical Activity
- Social Activity
- Spiritual Activity
- Meditation
- Control of Stress
- Humor/Attitude
Mediterranean Diet (Mostly Plants)

High Consumption of:
- Fruits (4-6 servings daily)
- Berries (flavanoids, phytochemicals)
- Vegetables (4-6 servings daily)
- Beans (3-6 servings daily)
- Nuts (3-5 pieces)
- Whole grains (3-6 servings daily)
- Olive oil (monounsaturated fatty acids)
- Fish – broiled not fried!
- Alcohol – red
- Spices (turmeric, ginger, garlic)

Low Consumption of:
- Saturated fat
- Dairy products
- Red meat and poultry

NEJM  June 26, 2003
Conclusions: Healthy Nutrition

- Eat fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products
- Include fish, beans, eggs, and nuts
- Water (24-40 ounces daily)
- Spices (turmeric, cinnamon, ginger, garlic)
- Chocolate?
- Low in saturated fats, *trans* fats, cholesterol, salt, and added sugars
- How healthy is your diet???????
Mediterranean Diet and Mild Cognitive Impairment

- 1393 community based, cognitively normal elders in New York

- 275 developed MCI during a mean follow up of 4.5 years

- Of those with MCI comparing to subjects in the lowest Med Diet adherence tertile
  - Middle tertile had a 45% less risk of converting to AD (p=0.01)
  - Those in the highest tertile had a 48% lower risk of converting to AD (p=0.02)

Physical Activity
Awesome Dancing Grandma

- http://www.youtube.com/watch?v=5qMCyyM_AtE
**Physical Activity, Diet and Risk of Alzheimer’s Disease**

- Prospective cohort study of 2 cohorts of 1880 community-dwelling elders without dementia in New York City
- Followed from 1992-2006
- Adherence to a Mediterranean-type diet and physical activity profile were measured, relative to correlation with time to incident AD
- 282 incident AD cases occurred during a mean of 5.4 yrs follow-up
- Both higher adherence to a Mediterranean-type diet (HR = 0.60, p = .008 for trend) and higher physical activity (HR = 0.67, p = 0.03 for trend) were independently associated with reduced risk for AD

Ref: Scarmeas N, et al. JAMA, Aug 12, 2009; 302(6)627-37
Physical Activity and Dementia Risk
Results from a Prospective Italian Study

- Prospective study of 749 subjects 65 years or older who were cognitively normal followed for 3.9 years

- 86 incident dementia cases (54 AD; 27 VaD)

- VaD risk was significantly lower for the upper tertiles of walking (HR=0.27), moderate (HR=0.29) and total physical activity (HR=0.24) compared to corresponding lowest tertile

- In this study physical activity is associated with lower risk of vascular dementia but not for AD

Physical Activity Reduces the Risk of Dementia in a Prospective European Study

- Findings are based on a prospective multinational European study that included yearly comprehensive assessments for 3 years including MRI.

- 639 subjects between the ages of 60-70 year old, 55% were women, 64% they were active at least 30 min daily three times a week.

- Phone interviews and clinical visits about depression, quality of life and ADL’s were used.

- The article shows that physical activity reduced the risk of VaD by 40% and cognitive impairment of any etiology by 60%.

Studies that Illuminate the Role of Physical Activity

- Stevens and Killeen (2006) demonstrated that 12 weeks of exercise (3x/week) on demented pts improve their performance on the Clock Drawing Test and Revised Elderly Persons Disability Scale compared to control and social interaction.

- Adlard et al (2005) demonstrated that five months of exercise decrease amyloid plaques in frontal cortex and hippocampus. Showed enhanced rate of learning on the Morris water maze and decrease escape latencies over 1\textsuperscript{st} 3-6 days of trial. The proposed mechanism: neuronal metabolism change that affects APP processing.
  - J of Neuroscience 25 (17) 4217-4221
More Evidence for Physical Activity

- Friedland et al (2001) patients with less cognitive and physically active at midlife had 250% increase risk for developing AD

- Laurin et al (2001) highest activity group had 60% less incidence of AD

- Rovio et al (2005) as little as 2x/wk leisure time activity decrease risk for dementia and AD

- Larson et al (2006) incidence of dementia 13/1000 person years for 3x/wk compared to 19.7/1000 person years for less than 3x/week
Exercise Training Increases Size of Hippocampus

- Single-blind, RC trial of 120 older adults assigned to two groups: moderate intensity aerobic exercise 3 days/week or stretching and toning exercises for one year.
- MRI before and after and BDNF levels were measured.
- Aerobic exercise increased anterior hippocampal volume after one year leading to improved memory and was associated with greater serum levels of BDNF (mediates in cell proliferation in the dentate gyrus of hippocampus).
- In summary, the one year of aerobic exercise was sufficient to increase the hippocampal volume by 2% so is never too late!

  - Erickson K et al. PNAS, Feb 2011, Vol. 108:3017-3022
Physical, Mental, and Social Activity Stave Off Dementia!

Study after study has demonstrated that staying physically active is one of the best ways to protect your brain.

Mental activity is equally important to brain health. So exercise your brain!

Research has also shown that socially connected people are less likely to develop dementia than their isolated peers.
Road to Successful Aging

- Social Activity- join groups, discuss topics, travel with friends
- Spiritual Belief System
- Mental Activity – learn something new (language, game, music, instrument, dance, video games, computers..)
- Meditation (Mindfulness, Transcendental)
- Yoga, Tai-chi
- “Growing old is mandatory; growing up is optional”
  - Chili Davis
Examining the Association Between Participation in Late-life Leisure Activity and Cognitive Function in Community-dwelling Elderly Chinese in Hong Kong

- 512 participants 60 years or older
- Four categories of leisure time activities
  - physical
  - intellectual
  - social
  - recreational
- Higher levels of leisure-time activity, in particular, intellectual activity, were associated with better cognitive function

Ref: Leung GT, et al. Int Psychogeriatr, Feb 2010; 22(1)2-13
Religiosity & Spiritual Support

- Religious participation enables elderly people to cope with and overcome emotional and physical problems more effectively, leading to a heightened sense of well-being in late adulthood.

- Less depression, lower risk of death after cardiac surgery, suicide is four times less likely.

- Exact mechanism is unclear
  - Positive emotions to stimulate the immune system
  - Better access to social and psychological resources
Example of Healthy Brain Aging

Madame Jeanne Calment 1875-1995

5 Lifestyle Secrets: Exercise, Nutrition, Stress Control, Social Activities, Great Sense of Humor!

“If you can’t do anything about it, don’t worry”

“I’ve never had but one wrinkle and I am sitting on it”
HEALTHY BRAIN AGING: CONCLUSIONS

- AD is the result of a variety of underlying pathological process and some can be modifiable.

- There is evidence that reducing the modifiable risk factors (lowering cholesterol and blood pressure, controlling diabetes, cutting nicotine and controlling alcohol consumption) promotes healthy brain aging and prevent dementia.

- Lifestyle changes should be implemented as part of our treatment plan with patients/families.

- Improving physical, nutritional and social activities decreases the risk of dementia and reduces mortality.

- Lifestyle modification works so let’s start making the changes now so we can improve our future!
Life matters!