Cardiovascular Health and Memory Loss: The Role of Exercise for Prevention and Treatment

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- **Consultant/Investigator:**
  - Plasma Exchange using Albutein (albumin) in mild to moderate AD: Grifols International Inc.
  - Member, Data and Safety Monitoring Board (DSMB): Accera
  - Scientific Advisory Board, Baxter: F-18 ligand
  - Speakers Bureau: Novartis

- **Steering Committee Member:**
  - Alzheimer’s Disease Neuroimaging Initiatives (ADNI).
  - Alzheimer’s Disease Cooperative Study

- **Advisory Council:**
  - Member, National Coalition on Alzheimer’s Disease.
Objectives

• Describe the impact of cardiovascular health on cognition

• Define the role of exercise in prevention and treatment of cognitive impairment
Dementia

• Acquired syndrome of gradual decline in memory, sufficient to affect daily life in a relatively well person.
  – At least deficiency in one other cognitive function:
    Language
    Visual spatial orientation or
    Executive function
    ❖ Not due to other medical, neurological, psychiatry condition or medication.
    ❖ Deficit not due to delirium
First Case:
57-Year-Old Woman with Memory Loss

Augusta D (Nov 3, 1906)
Dr. Solomon Carter Fuller authored the first published paper on AD in the English literature.

Prevalence of Alzheimer’s Disease (AD)

- Most common form of dementia (60-70%)
- 4th leading cause of death due to disease for people >65 in US
- Treatment Costs: $100 billion annually

Estimated Rates in The United States

Prevalence of Alzheimer's Disease (AD)

Current and Future Estimates of the Prevalence of Alzheimer’s Dementia in the World

- **1980**: Developed World - 6.5, Developing World - 5
- **2000 (est)**: Developed World - 8.5, Developing World - 11.5
- **2050 (est)**: Developed World - 10, Developing World - 25

Graph showing millions of Alzheimer’s dementia cases.
Predicted Percent Increase in Alzheimer’s Disease by Year 2050

Lower rates in:
- Asia
- Africa
- India

Higher rates in:
- African Americans and Hispanics than in Caucasians or Africans

Note: Based on estimated data for 2006 and 2050.

Alzheimer's disease Pathology

β-amyloids & Neurofibrillary tangles

β-amyloid (A type of protein):

- Toxic
- Enable the toxicity of other molecules
- Its deposition promotes inflammation that is harmful to brain cells
Alzheimer’s Disease: The Brain

- The brain has billions of neurons.
- To stay healthy, neurons must communicate with each other, carry out metabolism, and repair themselves.
- AD disrupts all three of these essential jobs.
Preclinical AD (MCI)

- Affected regions begin to **shrink** as **nerve cells die**.
- Changes can begin **10-20 years** before symptoms appear.
- **Memory loss**, the first visible sign, is the main feature of **mild cognitive impairment** (MCI).
- **MCI** is often the initial phase between normal aging and AD.
AD and the Brain

What’s the Difference Between Normal and MCI?

**Normal Aging**
- Loss of memory for words and names
- Slowed processing speed
- Difficulty sustaining attention when faced with competing environmental stimuli
- No functional impairment

**Mild Memory Loss (MCI)**
- Memory impairment beyond that expected for age, increasing over last 6 to 12 months
- Other cognitive functions generally unimpaired
- Daily function not significantly impaired
- Not dementia

*Source: Dr. Pierre Tariot, Banner Alzheimer’s Disease Institute, Phoenix, AZ.*

What is on The Horizon for Alzheimer’s Disease Research?
AD and the Brain: Mild Stage

- **AD spreads through the brain:** The cerebral cortex begins to shrink as more and more neurons stop working and die.

- **Mild AD signs:** can include memory loss, confusion, trouble handling money, poor judgment, mood changes, and increased anxiety.
Moderate AD

- As the brain shrinks as more and more neurons die

**Moderate AD signs:**
- Increased memory loss
- Confusion and problems **recognizing** people
- Language and thinking problems
- Restlessness and agitation
- Wandering and repetitive statements.
In severe AD: extreme shrinkage occurs in the brain. Patients are completely dependent on others for care.

Symptoms can include weight loss, seizures, groaning, moaning, or grunting, increased sleeping, loss of bladder and bowel control.

Death usually occurs from aspiration pneumonia or other infections.
Alzheimer's Disease

A 58 year-old man developed slowly progressive memory loss over two years. Initially he had difficulty remembering names and numbers. Later he frequently became lost while driving, and would forget to turn off the shower or the oven after using them.

Alzheimer's Disease. Coronal MRI scans. These two images were taken two years apart.

- Note generalized parenchymal volume loss, which is more marked in the second (later) image.
- Note that as the brain volume decreases, the volume of the CSF spaces compensates and becomes larger.
- Also note that the volume loss is somewhat asymmetric, being more prominent on the left side.
AD and the Brain

Brain Changes in Alzheimer’s Disease

- No one knows exactly what causes AD to begin
- But, we now know a lot about what happens in the brain after AD begins.

Pet Scan of Normal Brain

Pet Scan of Alzheimer’s Disease Brain
Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade, expanded in the preclinical phase to AD.
Development of Alzheimer Therapy

1910-1980
- Compassion
- Neurochemical Deficit (Cholinergic Hypothesis)
  - AChE Precursors and ACh Agonists
  - CholinesteraseInhibitors
  - NMDA Antagonists

1980s
- Systemic Deficiency (Amyloid Hypothesis)
  - Anti-inflammatories
  - Hormone Replacement
  - Anti-oxidants (e.g. Vit. E)

1990s
- Abnormal Folding of Protein (Refined Amyloid Hypothesis)
  - Anti-amyloid Agents
  - Immunotherapy
  - Prevention and CVD Risk

2000s and Beyond

- Tacrine
- Donepezil
- Rivastigmine
- Galantamine
- Memantine


RELKIN 2006
Ethnicity-Related Risk:
Cumulative Risk of AD in Relatives by Ethnic Groups (US Sample: The MIRAGE Study)
Established and Emerging Risk Factors for Alzheimer’s Disease

**Immutable Risk**
- Unchangeable risk factors
  - Age
  - Family History
  - APOE Gene
  - Female Gender
  - Ethnicity

**Mutable Risk**
Scientists also believe that the following preventable risk factors contribute to Alzheimer's disease risk
- Low Levels of Education
- Elevated Blood Pressure
- High Cholesterol/Inflammation
- Overweight and Obesity
- Cigarette Smoking
- Diabetes
- Lack of exercise (Sedentary Lifestyle)

Deposition of Abnormal Protein (Amyloid) Result in Alzheimer’s Disease

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Race, education, literacy, & incident AD

n = 1,192

** p < .01; *** p < .001

Manly et al., in preparation
Established Gene Markers for Alzheimer’s Disease

**Deterministic Mutations:**
- Amyloid Precursor Protein (APP)
- Presenilin-1 (PS-1)
- Presenilin-2 (PS-2)

**Susceptibility Polymorphism:**
- Apolipoprotein E (APOE)
Population Frequencies of APO E4 Allele: Most Important Genetic Risk Factor for Late-Onset AD

- Despite higher rates of occurrence of APOE4 in AAs compared to Whites, AD risk associated with E4 is less in AAs.
- But why?
Cholesterol Transport Gene: Implicated in AD with Greater Relevance for AAs

Variants in the ATP-Binding Cassette Transporter (ABCA7), Apolipoprotein E e4, and the Risk of Late-Onset Alzheimer Disease in African Americans

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Importance Genetic variants associated with susceptibility to late-onset Alzheimer disease are known for individuals of European ancestry, but whether the same or different variants account for the genetic risk of Alzheimer disease in African American individuals is unknown. Identification of disease-associated variants helps identify targets for earlier diagnosis, prevention, and treatment.

Objective To identify genetic variants associated with late-onset Alzheimer disease in African Americans.

Design, Setting, and Participants The Alzheimer Disease Genetics Consortium (ADGC) assembled multiple data sets representing a total of 3996 African American (1068 case participants, 2928 control participants) 60 years or older who were enrolled between 1989 and 2011 at multiple sites. The association of Alzheimer disease with genotyped and imputed single-nucleotide polymorphisms (SNPs) was assessed in case-control and family-based data sets. Results from individual data sets were combined to perform inverse variance-weighted meta-analysis, followed by genome-wide analyses and subsequently with gene-based tests for previously reported loci.

Main Outcomes and Measures Presence of Alzheimer disease according to standardized criteria.

Results Genome-wide significance in fully adjusted models (age, APOE genotype, population stratification) was observed in SNP rs45580098 (0.02; OR, 0.87; 95% CI, 0.82-0.93; P=2.2×10^-8) in linkage disequilibrium with APOE e4 previously associated with Alzheimer disease in European ancestry (OR, 1.3; 95% CI, 1.2-1.4; P=4.7×10^-7) and rs4747339 (0.02; OR, 0.87; 95% CI, 0.82-0.93; P=2.2×10^-8), which is in linkage disequilibrium with SNP previously associated with Alzheimer disease in European ancestry (OR, 1.3; 95% CI, 1.2-1.4; P=4.7×10^-7). The effect size for the SNP in ACA7 was comparable with that of the APOE e4-risk SNP rs429358 (OR, 0.36; 95% CI, 0.28-0.45; P=1.8×10^-5). Several loci previously associated with Alzheimer disease but not reaching genome-wide significance were replicated in gene-based analyses, including rs4747339 (OR, 0.87; 95% CI, 0.82-0.93; P=2.2×10^-8).

Conclusions and Relevance In this meta-analysis of data from African American participants, Alzheimer disease was significantly associated with variants in ACA7 and with other genes that have been associated with Alzheimer disease in individuals of European ancestry. Replication and functional validation of this finding is needed before this information is used in clinical settings.
Percent Rates of Dementia in the Yorubas and African Americans

Rates of Vascular Risk Factors in Two Black Populations (United States vs. Nigeria)

Mean BMI

Mean SBP and Cholesterol levels

Percent with Hx of HTN, Diabetes, and Stroke

Note: BMI--body mass index; SBP--systolic blood pressure; HTN--hypertension

Cardiovascular Risk Factors and Risk of Dementia

Final model adjusted for: age, sex, years of education, intelligence, hypertension, thyroid disorder, self-rated health, smoking, and baseline MMSE score

Cardiovascular Risk Factors and Risk of Dementia

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Mean Short Portable Mini-Mental State Examination Score by Blood Pressure Categories in Different Age-Groups

Obisesan TO et al, JAGs 2008
Association of Hypertension with Neurocognitive Loss (NHANES III)

**Mean Short Portable Mini-Mental State Examination (SHP-MMSE) score adjusted for age, gender, ethnicity, education, income, and pulse pressure**

*Obisesan et al. JAGS 2008*
Interaction of APOE Gene with Blood Pressure: Their Combined Effects on Hippocampal Volume (ADNI Study)

Figure 1: Least Square Means (LSMEANS) Hippocampal Volume by JNC Categories of Hypertension (JNC1 is slightly modified to differentiate those with low blood pressure)

- Normal
- Prehypertension (JNC2)
- Stage 1 Hypertension (JNC3)
- Stage 2 Hypertension (JNC4)

Categories:
- JNC1
- Normal
- EMCI
- LMCI
- AD

Legend:
- JNC Categories of Hypertension (E4 Negative)
- JNC Categories of Hypertension (E4 Positive)

Obisesan TO et al, AAIC 2013
Cardiovascular System and The Brain
Is Oxygen and Nutrient Supply Critical?

- Remove CO2 and metabolic products
- Transport glucose and micronutrients

Other Important Functions of Cerebral blood flow:

- Consumes: 20% of total body Oxygen supply
- Translates into high metabolic demand
- Receives: 15% of total cardiac output
- Approximates 2% of body weight

The Brain:

• What exactly causes Alzheimer’s disease to begin we do not know?
Can Aerobic Exercise-Training Improve Memory?
Physical activity associated with:

- 42% reduction in the odds of cognitive impairment (OR=0.58; 95% CI 0.41-0.83)
- 50% reduction in the odds of Alzheimer’s disease (OR 0.50; 95% CI 0.28-0.90)
- 37% reduction in the odds of dementia of any type (OR 0.63; 95% CI 0.40-0.98)

(Laurin DR et al Neurol 2001)
• Meta-analysis of 18 studies in non-demented adults: Fitness adaptation associated with enhance cognitive processes (Colcombe et al Psychol Sci 2003)
Mean 6-Year Decline in Modified mMmSE Scores by Baseline Tertiles of Peak VO2 (mm/kg/min)
(Sample =349; Age= >55 years)

Adjusted MMSE Decline

Final model adjusted for: age, sex, years of education, intelligence, hypertension, thyroid disorder, self-rated health, smoking, and baseline MMSE score
Aerobic Fitness and Cognition
(Sample=5925; Age ≥ 65)

- 8-Year prospective study in women showed that: Fitness adaptation associated with reduction in the decline on cognitive test (Yaffe et al Arch Intern Med 2001)

- Percentage decline in age-adjusted modified Mini-Mental State Examination (mMMSE) score during the 6- to 8-year follow-up as a function of physical activity (blocks [1 block 160 m] walked).
  - The difference between women in the higher quartiles and those in the lower quartiles was significant ($P<.001$).
The association of physical activity with cognition according to the presence of E4

Memory Function by Aerobic-Related Physical Activity Within APOE Genotype Group (Age 60-69)

Obisesan et al. 2009
Memory Function by Aerobic-Related Physical Activity Within APOE Genotype Group (Age >70)

Obisesan et al. 2009
A recent 24-Week randomized control trial of unsupervised physical activity study, showed: 2.3 change in ADAS-cog at follow-up.

- Sample=170
- 138 completed 18 month assessment

(Lautenschlaner JAMA 2008)
In What Ways Might Aerobic Exercise Exert Its Effects on Memory
Mechanisms Underlying the Effects of Fitness Adaptation on Memory?

- Promote neurotrophic changes
- Nerve cell regeneration
- Neurotransmitter repletion
- Reduce stress hormone such as cortisol
- Susceptibility of putative AD risk factors to lifestyle alterations
  - Training-related improvements in CVD risk factors and Cognitive Processes?
Aerobic Fitness and AD: Postulated Mechanism

AERobic EXercise/PHYSICAL ACTIVITY

- Favorably affects lipids
- Favorably affects inflammation
- Favorably affects blood pressure
- Favorably affects glucose homeostasis

- Increase HDL-C
- Decrease total cholesterol
- Reduce CRP levels
- Reduce interleukins
- Improves endothelia function
- Improves arterial compliance
- Improves glucose homeostasis
- Downregulates HIF-1 during hypoglycemia

Reduce vascular inflammation, endothelia damage, and angiopathy, and improves vascular compliance

Reduce arteriolar sclerosis (small vessel disease)

Increased cerebral perfusion and oxygenation

Decreased amyloid deposition and possibly tauopathy

Improved cognition

Note: Aerobic exercise increase HDL-C and subfractions; decrease total cholesterol, C-reactive protein and interleukin_1; improves endothelia function and arterial compliance; improves glucose homeostasis and down-regulate hypoxia-
HDL Cholesterol, Physical Activity and Cognition (NHANES III)

Obisesan et al, 2009, ICAD Vienna Austria
Training-Induced Changes in Large Particle Size HDL Cholesterol by APOE Genotype In Blacks (6-Month Aerobic Exercise-Training)

Obisesan et al, Metabolism 2008
6-Month Aerobic Exercise Training-Induced Changes in C-Reactive Protein (CRP) by 732/+219 Haplotype of the CRP Gene

Obisesan et al, Arteriosclerosis, Thrombosis and Vascular Biology 2007
Aerobic Exercise Enhanced Glucose Disposal & Reduce Cortisol Levels in Mild Cognitive Impaired Women in Controlled Clinical Trial (Sample=17 women; Age 55-85)

Figure 3. Mean (standard error of the mean) values representing the change from baseline for physiological measures, expressed as residual scores. Insulin sensitivity, estimated by glucose disposal (glucose [mL]/insulin [mIU/kg]) during the 30-minute steady-state period of hyperinsulinemic-euglycemic clamp (A) and by homeostasis model assessment (HOMA) (B) improved for women in the aerobic group (glucose disposal $P=.005$; HOMA $P=.04$). Aerobic exercise had different effects on plasma levels of cortisol (C) and brain-derived neurotrophic factor (BDNF) (D) for women and men ($group \times sex$ cortisol, $P=.02$; BDNF, $P=.04$). Relative to controls, aerobic exercise reduced cortisol and BDNF levels for women (cortisol, $P=.05$; BDNF, $P=.06$) and increased levels for men (cortisol, $P<.04$; BDNF, $P=.10$). Levels of BDNF were adjusted for platelet factor 4 levels and baseline insulin sensitivity. *$P<.05$; **$P<.01$; †$P<.1$. 

Baker LD et al. Arch Neurolo Jan 2010
Exercise lowers Aβ level in Mice and Levels of IL-1β in transgenic mice

Nichol et al, Neuroinflammatory April 2008
Aerobic Fitness Reduces Brain Tissue Loss in Aging Humans

Limitation of Previous Studies Testing the Effects of Aerobic Exercise on Memory

• Limited number of prospective studies were non-supervised, and therefore unable to:
  • Accurately quantify the volume of exercise that is beneficial
  • Did not examine the mechanisms underlying exercise effects
  • Included mostly Caucasians
Ongoing Study: Effects of a 6-Month Aerobic Exercise-Training on Memory

Primary objective: To determine whether 6 months aerobic exercise-training can improve cognition in older African American MCI subjects

Obisesan TO
Summary: Alzheimer’s Disease, CVD Risks and Prevention

• Multiple risk factors are likely involved in AD
• Genetics
  • Presenilin 1 and 2 mutations: early onset disease
  • APOE: Most consistent non-deterministic genetic risk factor
    o Reduced contribution to AD risk in AAs
• CVD risk likely contribute to overall AD risk
• AAs harbor disproportionately higher rates of CVD risks
  • ? Greater contribution of CVD risk to AD in AAs
• Lifestyle changes can:
  • Reduce CVD risks
  • Likely enhance cognitive wellness
Prevention: The 12 Dos: Put on Your “To Do List”

- Weight reduction if overweight or obese
- Increased physical activity
- Control blood sugar
- Control blood pressure
- Control cholesterol levels
- Good and balanced nutrition
- Stop smoking
- Do not drink excessive amount of alcohol
- Brain aerobics
- Socialize
- Get treatment if depressed
- Avoid stress
"Memory....without it ... all life and thought were an unrelated succession. As gravity holds matter from flying off into space, so memory gives stability to knowledge; it is the cohesion which keeps things from falling into a lump or flowing in wave...

Memory performs the impossible for man by the strength of his divine arms; holds together past and present, beholding both, existing in both, abides in the flowing, and gives continuity and dignity to human life. It holds us to our family, to our friends. Hereby a home is possible...."

Ralph Waldo Emerson (1803-1882)
11.12. 1879, age 76