Minimizing Your Risk for Alzheimer’s Disease

Mehul Trivedi, PhD,
Assistant Professor, Department of Psychiatry
SIU School of Medicine, Springfield, IL.

03 May 2019

No Financial Disclosures

LEARNING OBJECTIVES

• Identify hereditary and lifestyle risk factors associated with increased risk for Alzheimer’s disease (AD).

• Highlight current research focused on understanding preclinical neurobiological and cognitive changes in individuals at risk for AD.

• Provide a brief overview of current clinical trials focused on delaying or preventing the onset of AD.
ALZHEIMER’S DISEASE

- Progressive neurodegenerative condition.
- Most common form of dementia in persons 65 and older (70%).
- Episodic memory is first and worst.
  - Other cognitive and/or behavior problems begin to emerge later.
    - Language, executive functions, visuospatial skills, personality changes, etc.
- Memory and other cognitive problems are significant enough to disrupt instrumental daily living skills (IADLs)
  - Shopping, housekeeping, accounting, food preparation/meds, telephone/transportation.

NEUROPATHOLOGY OF AD

Beta Amyloid Plaques and Neurofibrillary Tangles are the Hallmarks of AD

ATROPHY IN AD
IN-VIVO NEUROIMAGING IN AD

- Preclinical phase: Brain changes begin in midlife, 10-20 years before cognitive decline in individuals at greater risk for AD.

RISK FACTORS FOR AD

- Clinical risk factors.
  - Amnestic mild cognitive impairment.

- Non-modifiable risk factors.

- Modifiable risk factors.

MILD COGNITIVE IMPAIRMENT

- Amnestic Mild Cognitive Impairment (aMCI)
  - Impairments in learning/memory that are not significant enough to significantly disrupt IADLs.

  - Continuum Perspective: Every patient with AD goes through an aMCI phase, but not every patient with aMCI goes on to develop AD.
    - aMCI: annual conversion rate to AD of 10-15%
    - A small percentage of individuals with aMCI, remain aMCI for years without converting to AD, others revert back to normal.
    - Time course of decline is not consistent.

- aMCI might be too late in the disease process to prevent decline to AD.
A CONTINUUM PERSPECTIVE

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NON-MODIFIABLE RISK FACTORS

- INCREASING AGE: #1 risk factor for late-onset AD
NON-MODIFIABLE RISK FACTORS

• FAMILY HISTORY OF AD

• People without a family history also develop AD.
• But, having a parent or sibling with AD increases risk for developing AD.
  • The more relatives with AD, the greater the risk.
  • Risk is much greater in children versus siblings.

NON-MODIFIABLE RISK FACTORS

• FAMILY HISTORY OF AD

NON-MODIFIABLE RISK FACTORS

• APOE GENOTYPE

• APOE gene is a protein involved in the metabolism of fats in the body.
• 3 alleles (e2, e3, e4), 6 genotypes.
• Inheriting one copy of the e4 allele
  • 3-fold increased risk of AD.
• Inheriting two copies of the e4 allele
  • 8-12-fold increased risk of AD.
• 20+ other genes increase risk for AD, none as great as the e4 allele (www.alzgene.org).
NON-MODIFIABLE RISK FACTORS

• INTERACTIVE EFFECTS
  • e4 allele is more prevalent in the children of individuals with AD.
    • 47% versus 21% in the general population (Wisconsin Registry for Alzheimer’s Prevention).
  • Lower age at onset of cognitive symptoms in e4 carriers.

GENDER

• More women than men have AD.
  • Not just related to longer life expectancy for women.
  • Almost two-thirds of US citizens with AD are women.

RACE AND ETHNICITY

• Older African-Americans and Hispanic Americans are about 1.5-2x more likely to develop AD compared to older not-Hispanic/White Americans.
RACE AND ETHNICITY

• APOE e4 allele less strongly associated with AD in African-Americans.

• Other genetic factors might be more strongly associated with greater risk for AD in African Americans.

• Modifiable risk factors, health disparities.
  • vascular comorbidities, level of educational attainment, quality of education, early life psychosocial stress, and other socioeconomic factors may account for some (but not all) of these differences.

COMPLEX INTERACTIONS AMONG NON-MODIFIABLE RISK FACTORS

MODIFIABLE RISK FACTORS FOR AD

• Up to 50% of all cases of AD may be due to potentially modifiable AD risk factors.

• Midlife: a critical period where many modifiable risk factors influence the development of AD later in life.
  • Supported by epidemiological, neuropsychological, and neuroimaging studies.
WHAT'S GOOD FOR THE HEART IS GOOD FOR THE MIND

MODIFIABLE RISK FACTORS FOR AD ARE ALSO CARDIOVASCULAR AND STROKE RISK FACTORS

• Modifiable risk factors tend to aggregate in individuals.
• **Metabolic syndrome**: 3 or more of hypertension, obesity, hyperlipidemia, diabetes.

DO RISK FACTORS FOR ALZHEIMER'S DISEASE IN MIDLIFE PREDICT CONVERSION TO DEMENTIA IN LATE LIFE?

Midlife risk score for the prediction of dementia four decades later
Klaus C. Fratiglioni, Charles F. Quesenberry, Jr., Ailin Banner, Min Kopito,
Gert Jan Berends, Rachel A. Whitmer

**CAIDE risk factor score**: sex, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, current smoking status, physical activity level, age and education.

- age, education, hypertension, BMI, and hyperlipidemia in midlife predicted the development of dementia four decades later.
- central obesity, depressed mood, diabetes mellitus, history of head trauma, lung function, and smoking did not improve prediction.
IS MIDLIFE A CRITICAL PERIOD IN THE DEVELOPMENT OF AD IN LATE LIFE?

Review Article

Is late-onset Alzheimer’s disease really a disease of midlife?

Korin Richi(1), Craig W. Richi(1), Kristin Vafei, Ignas Skripa, Nikolai Scarmeas(1,2)

(1) Department of Rehabilitation Medicine, Columbia University, New York, NY, USA
(2) Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA

• Considerable evidence suggests that exposure to AD risk factors and brain changes appear to already be present in midlife.
• Promotion of cardiovascular health during midlife in persons with a family history of AD may considerably reduce disease risk.
• Strong need for dedicated prospective biomarker studies in middle-age, at-risk populations.


CAIDE APP

PROSPECTIVE, COHORT STUDIES IN MIDDLE AGED INDIVIDUALS AT RISK FOR AD

- Not many, very expensive, very long follow-up time.

- Wisconsin Registry for Alzheimer’s Prevention (WRAP)

WISCONSIN REGISTRY FOR ALZHEIMER’S PREVENTION (WRAP)

Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer’s disease

Elizabeth A. Boots, Stephanie A. Schulte, Jennifer M. Ob., Jordan Larson, -

Kathryn Edwards, Sarah Cook, Rebecca L. Kowch, -

Marissa H. Bedingfield, Catherine S. Gallagher, Cynthia M. Cashmore, Howard A. Raskin, -

Barbara B. Bedell, Annalisa Lallia, -

Brian A. Herbert, -

Mark A. Sager, -

Stefani C. Johnson, -

Olivia C. Rundio, -

Meeting physical activity recommendations may be protective against temporal lobe atrophy in older adults at risk for Alzheimer’s disease

Ryan J. Dougherty, -

Laura D. Elkind, -

Stephanie A. Schulte, -

Elizabeth A. Boots, -

Jacqueline D. Meyers, -

Jennifer B. Lindheimer, -

Stephanie Van Hoye, -

Aaron J. Rogerson, -

Kathryn P. Labadie, -

Jennifer M. Ob., -

Rebecca L. Kowch, -

Marissa H. Bedingfield, -

Catherine S. Gallagher, -

Cynthia M. Cashmore, -

Howard A. Raskin, -

Brian A. Herbert, -

Mark A. Sager, -

Stefani C. Johnson, -

Olivia C. Rundio, -

Bruce R. Cook, -

Booth et al., 2014, Dougherty et al., 2016

INTERVENTIONS TO PREVENT COGNITIVE DECLINE

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• 263 eligible studies (primarily in older adults); 13 classes of interventions were identified:
  • cognitive training
  • physical activity
  • nutraceuticals
  • diet
  • multimodal interventions
  • hormone therapy
  • vitamins
  • antihypertensive treatment
  • lipid lowering treatment
  • nonsteroidal anti-inflammatory drugs (NSAIDs)
  • anti-dementia drugs
  • diabetes treatment
  • "other interventions"

INTERVENTIONS TO PREVENT COGNITIVE DECLINE

• NO high-strength evidence for any intervention to delay cognitive decline.

• Moderate-strength evidence that cognitive training improves performance in the domain that was trained (memory, processing speed) in older adults.
  • Benefits did not transfer to other cognitive areas.
  • Little evidence for benefit beyond 2 years after trial conclusion.

• Low-strength evidence for physical activity, antihypertensive medications, NSAIDs, B vitamins, nutraceuticals, and multimodal interventions.
  • Methodological limitations were prominent.
    • Lack of consistent cognitive outcome measures, longer follow-up duration needed, and participant attrition in longer duration interventions.

• Testing interventions that address modifiable risk factors can help to establish their causative role in MCI and AD.

FINGER STUDY

Recruitment and Baseline Characteristics of Participants in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)—A Randomized Controlled Lifestyle Trial

1.260 cognitively normal, older adults in Finland between the ages of 60-77 completed a 2-year multi-domain intervention (diet, exercise, cognitive training, vascular risk monitoring).

• Outcome measures: cognition, dementia (after extended follow-up), disability, vascular risk factors and outcomes, depressive symptoms, quality of life, and neuroimaging measures.

US POINTER STUDY

U.S. POINTER
A Lifestyle Intervention Trial to Support Brain Health and Prevent Cognitive Decline

Recruitment begins in 2018

The Alzheimer’s Association U.S. Study to Prevent Brain Health Through Lifestyle Intervention to Reduce Alzheimer’s Risk (U.S. POINTERS) is a 6-year, multi-site, randomized, controlled trial with 1,000 participants. The study aims to test a lifestyle intervention to improve brain health in older adults.

Intervention Methods will include:
- Physical Exercise
- Nutritional Counseling and Meal Planning
- Cognitive & Social Reconnection
- Support and Management of Mild Dementias

GRAY MATTERS STUDY

The design and progress of a multimodal lifestyle intervention to improve brain health in middle-aged persons to reduce later Alzheimer’s disease risk: The Gray Matters randomized trial

Gray Matters is a 5-year, multi-site, randomized, controlled trial with 200 participants. The study aims to test a lifestyle intervention to improve brain health in middle-aged adults.

- 6-month multimodal intervention conceptually similar to FINGER and POINTER studies but in middle-aged adults with much smaller sample size (N=144).
- Increase in positive health behavior changes across intervention trial was associated with improved vascular health:
  - Lower Body mass index
  - Higher HDL (good cholesterol)
  - Greater motivation to engage in physical activity and make healthy food choices.

GRAY MATTERS STUDY

http://graymattersapp.org/
COMPLEX INTERACTIONS BETWEEN MODIFIABLE AND NON-MODIFIABLE RISK FACTORS

Race/Ethnicity
Health
Family History
Age
Genetics
Gender
education

PRECISION MEDICINE AND AD RISK REDUCTION

- Precision Medicine is focused on identifying treatment approaches that will be effective for different groups of patients based on genetic, environmental, and lifestyle factors.

- Applying these evidence-based principles of precision medicine to tailor individualized recommendations, follow patients longitudinally to continually refine the interventions, and evaluate "N-of-1 effectiveness."

Formulation of evidence-based messages to promote the use of physical activity to prevent and manage Alzheimer's disease

"Regular participation in physical activity is associated with a reduced risk of developing Alzheimer's disease. Among older adults with Alzheimer's disease and other dementias, regular physical activity can improve performance of activities of daily living and mobility, and may improve general cognition and balance."
SUMMARY

- AD is the most common cause of age-related dementia.

- Non-modifiable and modifiable risk factors.

- Reducing prevalence rates of modifiable risk factors by 10-20% could reduce prevalence rates of AD by up to 15%.
  - Midlife is a critical period.

- Intervention studies to date have yet to produce high or moderate evidence to support their use in prevention of AD.

- Some support for physical activity and multimodal interventions in improving cognition in older adults.
  - FINGER and POINTER studies.

- Higher levels of physical activity are associated with improved vascular health and reduced AD biomarkers in middle aged adults at risk for AD.

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