Minimizing Your Risk for Alzheimer’s Disease

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08.November.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.

• Introduce recent clinical trials focused on delaying or preventing the onset of AD.

ALZHEIMER’S DISEASE (AD)

• Progressive neurodegenerative condition.

• Most common form of dementia in older adults (>65) (70%).

• 10% of individuals aged 65 or older have AD.

• Learning and remembering new information is the first and worst symptom.
  • 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.
PREVALENCE RATES ARE INCREASING OVER TIME

NEUROPATHOLOGY OF AD

Beta Amyloid Plaques and Neurofibrillary Tangles are the Hallmarks of AD

Normal vs. Alzheimer’s Diseased Brain

ATROPHY IN AD

Brain Atrophy in Advanced Alzheimer’s Disease

• A long preclinical phase where brain changes begin in middle age, 10-20 years before cognitive decline in individuals at greatest risk.

IN-VIVO NEUROIMAGING IN AD

Teipel et al., 2015
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 and remembering new information 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 variable.

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

Preclinical AD  MCI Due to AD  Dementia Due to AD

Asymptomatic  Symptomatic

Preclinical AD  MCI Due to AD  Dementia Due to AD

https://aspe.hhs.gov/advisory-council-april-2016-meeting-presentation-terminology-heterogeneity

A CONTINUUM PERSPECTIVE

Normal Aging  Everyone experiences slight cognitive changes during aging

Preclinical
- Silent phase: brain changes without measurable symptoms
- Individual may notice changes, but not detectable on tests
- "A stage where the patient knows, but the doctor doesn’t"

MCI
- Cognitive changes are of concern to individual and/or family
- One or more cognitive domains impaired significantly
- Preserved activities of daily living

Dementia
- Cognitive impairment severe enough to interfere with everyday abilities

Mild
Moderate
Moderately Severe
Severe

Time (Years)

NON-MODIFIABLE RISK FACTORS

• **INCREASING AGE**: #1 risk factor for late-onset AD

![Graph showing prevalence rates of AD by age](adapted Alzheimer's Association Facts and Figures 2019)

0% 5% 10% 15% 20% 25% 30% 35% 40% 45% 50%

<65 65-74 75-84 85+

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.
  • The more relatives with AD, the greater the risk.
  • Risk is greater in children versus siblings.
NON-MODIFIABLE RISK FACTORS

• FAMILY HISTORY OF AD

Incidence of Alzheimer's When Both Parents Have Disease Compared to the General Population

Data from: "Combined Alzheimer Disease Risk in Children Whose Both Parents Have Alzheimer Disease" - Archives of Neurology, 2009

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 is associated with increased risk for developing aMCI and AD.

Estimated percentages of the U.S. population with the six possible e2, e3, and e4 pairs of the apolipoprotein E (APOE) gene:

<table>
<thead>
<tr>
<th>APOE pair</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>e2/e2</td>
<td>0.5</td>
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<tr>
<td>e2/e3</td>
<td>11</td>
</tr>
<tr>
<td>e2/e4</td>
<td>2</td>
</tr>
<tr>
<td>e3/e3</td>
<td>6.1</td>
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<tr>
<td>e3/e4</td>
<td>23</td>
</tr>
<tr>
<td>e4/e4</td>
<td>2</td>
</tr>
</tbody>
</table>

NOTE: Created from data from Ruber and colleagues [20]. Percentages do not total 100 due to rounding.

- 20+ other genes increase risk for AD, none as great as the e4 allele (www.alzgene.org).

Alzheimer's Association Facts and Figures 2017
**NON-MODIFIABLE RISK FACTORS**

Approximate Lifetime Risk (%) of Alzheimer's Disease Based on ApoE Genotype*


**NON-MODIFIABLE RISK FACTORS**

**INDEPENDENT AND INTERACTIVE EFFECTS**

- APOE e4 allele is more common in the children of individuals with AD.
  - 47% (Wisconsin Registry for Alzheimer’s Prevention).
  - 27% in the general population.

- Lower age at onset of AD symptoms in e4 carriers.
GENDER

- Women are at greater risk for 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 1.5-2 times 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.
  • Variations in health, lifestyle and socioeconomic risk factors across racial groups likely account for most of the differences in risk for AD.

Alzheimer's Association Facts and Figures 2019

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.

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?

Karen Ritchie[^1,^2], Craig W. Ritchie[^3,^4], Kristine Yaffe[^5], Ingmar Skoog[^6], Nikolaos Scarmeas[^7,^8]

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- 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.

MODIFIABLE RISK FACTORS FOR AD

Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective

Matthew Baumgartn, Heather M. Snyder1, Maria C. Camillo2, Sam Fazii1, Hye Kim1, Harry Johns1
1Division of Public, Policy, and Health’s Department, Washington, DC 20501
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Fig. 1. Strength of evidence on risk factors for cognitive decline.

Baumgart et al. (2015) Alzheimer’s and Dementia, 11, 718-26
MODIFIABLE RISK FACTORS FOR AD

Potential for primary prevention of Alzheimer’s disease: an analysis of population-based data


- Modifiable risk factors tend to aggregate in individuals.
- **Metabolic syndrome**: 3 or more of hypertension, obesity, hyperlipidemia, diabetes.
WHAT’S GOOD FOR THE HEART IS GOOD FOR THE MIND

COMPLEX INTERACTIONS BETWEEN MODIFIABLE AND NON-MODIFIABLE RISK FACTORS
RISK FACTORS FOR ALZHEIMER’S DISEASE IN MIDLIFE PREDICT DEMENTIA IN LATE LIFE

Midlife risk score for the prediction of dementia four decades later
Lieza G. Exalto, Charles P. Quesenberry, Deborah Barnes, Miia Kivipelto, Geert Jan Biessels, Rachel A. Whitmer

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1University of California, San Francisco, CA, USA
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Higher aggregate CAIDE risk factor scores in midlife predict the development of dementia 40 years later.
• Age
• Education
• Hypertension
• Body mass index (BMI)
• Hyperlipidemia

Associations of CAIDE Dementia Risk Score with MRI, PIB-PET measures, and cognition

Higher CAIDE scores at midlife are associated with Alzheimer’s disease brain changes 30 years later.
• Greater white matter disease
• Reduced cortical and hippocampal volume
• Worse cognitive function.
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. Schultz • Jennifer M. Oh • Jordan Larson • Dorothy Edwards • Dane Cook • Rebecca L. Koscié • Maritza N. Dowling • Catherine L. Gallagher • Cynthia M. Carlson • Howard A. Rowley • Barbara B. Bendlin • Asenath LaRue • Sanjay Asthana • Bruce P. Hermann • Mark A. Sager • Sterling C. Johnson • Ozioma C. Okonkwo

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. Ellingson•, Stephanie A. Schultz•, Elizabeth A. Boots•, Jacob D. Meyer•, Jacob B. Lindheimer•, Stephanie Van Riper•, Aaron J. Stegner•, Dorothy F. Edwards•, Jennifer M. Oh•, Rebecca L. Koscié•, Maritza N. Dowling•, Catherine L. Gallagher•, Cynthia M. Carlson•, Howard A. Rowley•, Barbara B. Bendlin•, Sanjay Asthana•, Bruce P. Hermann•, Mark A. Sager•, Sterling C. Johnson•, Ozioma C. Okonkwo•, Dane B. Cook•

Boots et al., 2014, Dougherty et al., 2016

INTERVENTIONS TO PREVENT COGNITIVE DECLINE

Comparative Effectiveness Review

Number 188

Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
500 Independence Ave, Stop 1475
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Colin Calvert, R.N.
Edward Rainer, M.D.
Lanc S. Horvitz, Ph.D.
Terry Breslow, Ph.D., L.P.

INTERVENTIONS TO PREVENT COGNITIVE DECLINE

• 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”

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

• Moderate-strength evidence that cognitive training in older adults improves performance in the domain that was trained (memory, processing speed).
  • 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.

• Recommended 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

Tia Ngandu 1,2,2, Jenni Lehtisalo 1, Esko Levilähti 1, Tiina Laatikainen 1,3,4,5, Jaana Lindström 1,5, Markka Peltola 1, Alina Solomon 3,6,7, Satu Ahlthuoto 1, Ritva Antikainen 1,7,8,
Tuomo Hänninen 9, Antti Jula 1, Francesca Mangialasche 9, Teemu Paajanen 3,4,
Satu Pajala 1, Rainer Rauramaa 1, Tiina Strandberg 4.5.9, Jaakko Tuomilehto 4.5.6,10,11
Hilkka Soininen 12,13 and Milla Kivipelto 1,2,4,9

- 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.


A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levilähti, Satu Ahlthuoto, Ritva Antikainen, Leo Räikkönen, Antti Jula, Tiina Laatikainen, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Martti Paanikka, Rainer Rauramaa, Anna Viikari-Juntura, Tia Ngandu, Jaakko Tuomilehto, Hilkka Soininen, Milla Kivipelto

Figure 2: Change in cognitive performance during the 2-year intervention
Recruitment began in 2018

WORLD WIDE FINGERS

A GLOBAL COLLABORATION FOR FUTURE GENERATIONS

The World Wide FINGERS (WW-FINGERS) is an interdisciplinary network to share experiences, harmonize data and plan joint international initiatives for the prevention of cognitive impairment or dementia.
WORLD WIDE FINGERS

https://www.coalitionforbetterhealth.org/advisors_partners

GRAY MATTERS STUDY

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

Maria C. Norton1,*, Christine J. Clark1,*, JoAnn T. Tschann2, Phillip Hartin3, Elizabeth B. Fauth3, Julie A. Gao4, Travis E. Dorsch5,*, Heidi Wengreen1, Chris Negant5, W. David Robinson1, Michael Levee1, Sally McClendon1, Ian Cleland1, Sydney Y. Schaefer6, Sheryl Aguilair

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2Department of Psychology, Utah State University, Logan, UT, USA
3School of Exercise and Nutrition Sciences, University of the West of England, Bristol, UK
4Department of Health, Physical Education and Recreation, Utah State University, Logan, UT, USA
5Department of Radiology and Nuclear Medicine, Utah State University, Logan, UT, USA
6School of Computing and Information Engineering, University of Ulster, Londonderry, UK

- 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.
GRA Y MATTERS STUDY

http://graymattersapp.org/

PRECISION MEDICINE AND RISK REDUCTION

- Precision Medicine is focused on identifying treatment approaches for chronic diseases 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.”

- Preliminary results (N=600) suggest that the clinical practice of AD risk reduction is feasible with measurable improvements in cognition and biomarkers of AD risk.
INDIVIDUALIZED CLINICAL MANAGEMENT OF PATIENTS AT RISK FOR AD

- Multimodal individualized intervention focused on patient education, genetic counseling, pharmacological approaches, nonpharmacological approaches in individuals with AD risk factors (N=174).

- Cognition, AD/vascular risk factors, and serum biomarkers were measured at baseline and after 18-month follow-up.

- Individuals in the intervention group demonstrated improved cognition and reduced AD/vascular risk factor scores.

PREVALENCE OF PRECLINICAL AD

- 6.08 million with AD or mild cognitive impairment due to AD in 2017.

- 46.7 million Americans with preclinical AD including amyloidosis, neurodegeneration, or both.

- Critical need for both primary prevention in individuals without preclinical AD and secondary prevention of developing AD in individual with preclinical AD.
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.
REFERENCES


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