Healthy Arizona
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A PUBLIC HEALTH INITIATIVE

HEALTHY ARIZONA WORKSITES PROGRAM (HAWP) PRESENTS:

WHAT STEPS CAN I TAKE TO PREVENT DEMENTIA?

Presented by:

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WEBINAR HOUSEKEEPING

WELCOME

All lines have been muted.

Please type any questions into the chat or Questions panel and we will do our best to answer them all at the end.

All handouts and a copy of the presentation slides are available in the Handouts panel.

Please complete the survey that will be emailed out after the presentation

A recording will be added to the library of HAWP webinars on our website within 48 hours.

Special thanks to our supporting partner Dignity Health for their generous support in making this webinar possible.

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Q&A

PLEASE ENTER YOUR QUESTIONS IN THE CHAT.

What specific steps can I take to prevent Dementia?

Yonas E. Geda, MD, MSc.
Professor and Director, Behavioral Neurology and Neuropsychiatry Fellowship Program.
Barrow Neurological Institute.
April 21, 2022

BARROW Neurological Institute

Dignity Health. St. Joseph's Hospital and Medical Center

Outline

- Alzheimer's Disease and related dementias
- Diagnosis and treatment of dementia
- Screening for dementia, referral to Neuropsychology, Biomarkers
- Treatment: Cholinomimetic agents and NMDA receptor (Memantine)
  - This will not be discussed
- Non-modifiable risk factors
- Lifestyle factors
  - Leisurely walk
  - Insulin
  - Mental activities
  - Emotions, cognition and behavior (e.g., behavioral variant FTD)

Are we facing a looming public health crisis?.

- Approximately 6.08 million Americans had either clinical AD or mild cognitive impairment due to AD in 2017
- It will grow to 15.0 million by 2060.
- In 2017, 46.7 million Americans had preclinical AD (amyloidosis, neurodegeneration, or both), although many may not progress to clinical disease during their lifetimes.
- Primary and secondary preventions have differential impact on future disease burden.
  - Brookmeyer R, Abdalla N, Kawas CH, Corrada MM. Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. Alzheimers Dement. 2018 ; 14:121-129.

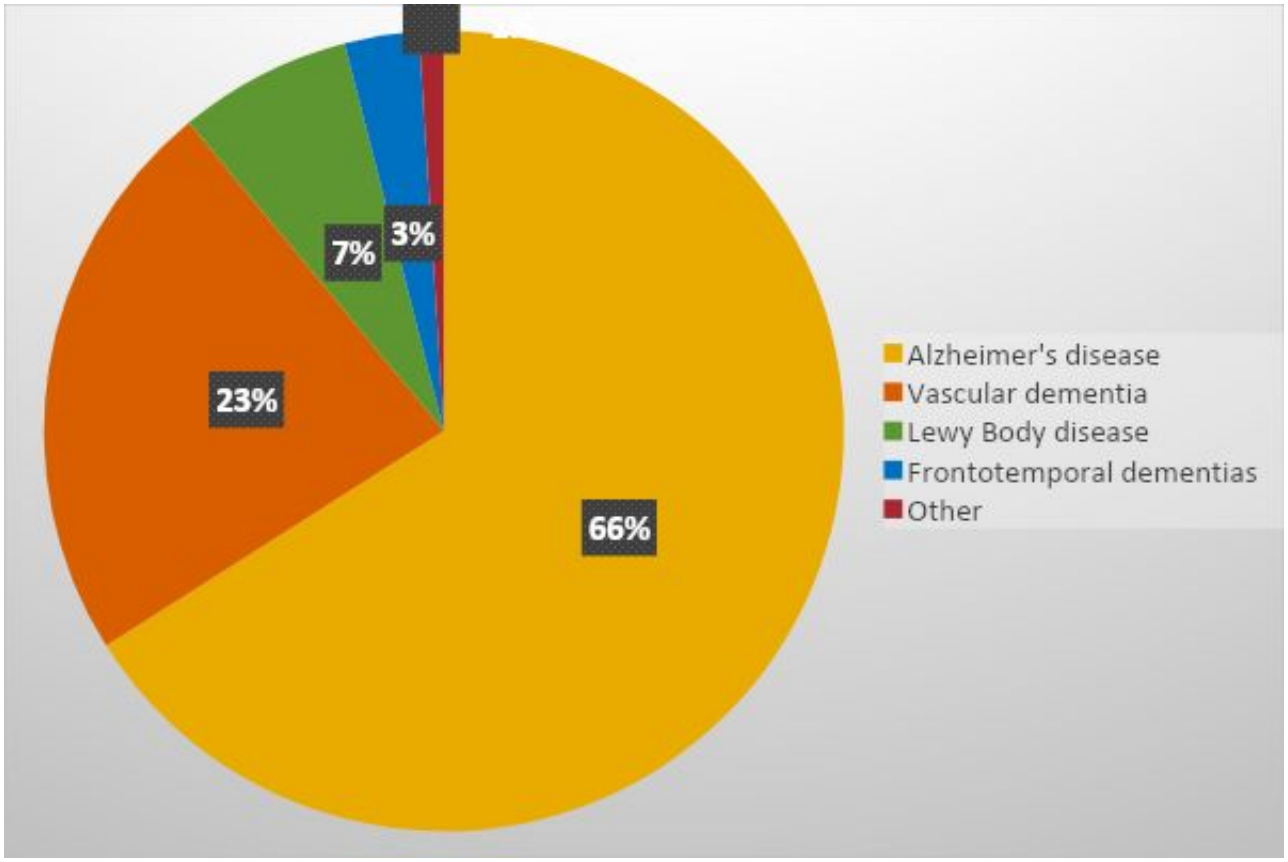
What is Dementia?

- Cognitive Impairment + Functional decline = Dementia
  - Cognitive domains: Memory domain, Language, Executive/Attention domain, Visuospatial/Sense of direction
    - Left hemisphere dominant Language, Right Hemisphere dominant visuospatial/sense of direction, frontal lobe, middle of the brain
      - Motor : basal ganglia – Alternate Motion Rate (AMR) exercise
        - Brain Stem – vital centers : breathing center, cardiac center, coughing center etc.
- Instrumental Activities of Daily Living: e.g. handling finances
  - Basic Activities of Daily living, e.g. taking shower, changing clothes, toileting

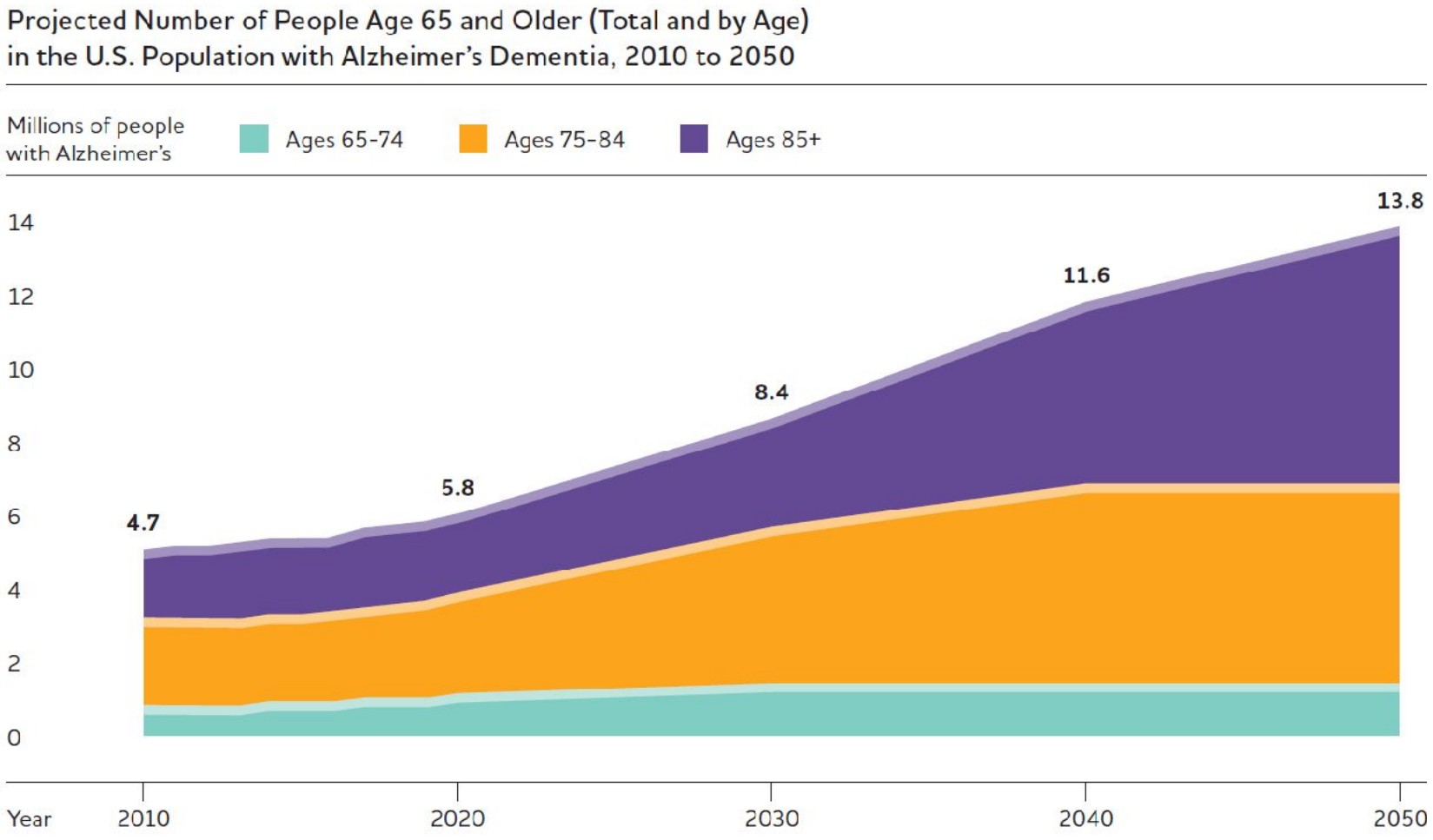
What are the different types of dementia?

- Out of 100 persons with dementia (degenerative dementia), about 70 have Alzheimer’s Dementia, about 10 of them have Lewy Body Dementia, the remaining are Frontotemporal Lobar degeneration etc.
- The most common cause of dementia: Neurodegeneration diseases e.g., Alzheimer's dementia
- Dementia can be caused by stroke, repetitive head injury, and metabolic disorders
- Degenerative dementias
  - Normal aging, mild cognitive impairment and dementia
    - The intermediate stage between normal aging and dementia

Prevalence of neurodegenerative dementias



Projected number of persons with Alzheimer‘s dementia



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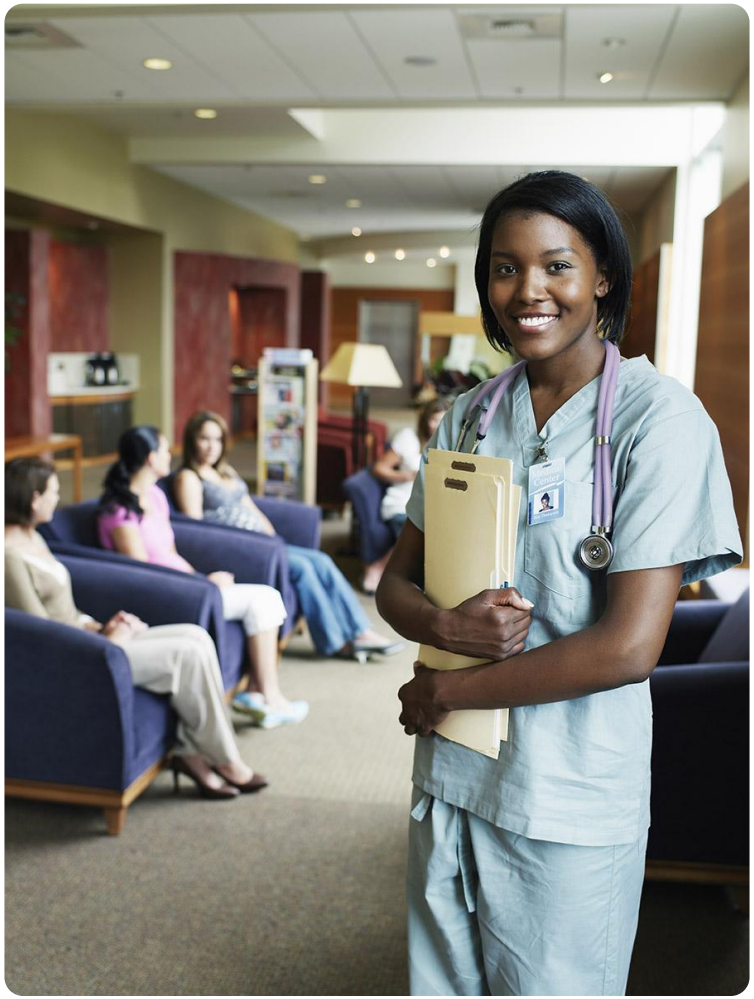
Pictures of the faculty at Tubingen (Alois Alzheimer's and others)

Fig. 16. On the Starnberg lake, from left to right: Alzheimer, Kraepelin, Gaupp, Nissl (about 1908)

Gastärzte im anatomischen Laboratorium; obere Reihe von links: F. Lotmar, unbek., St. Rosental, Allers(?), unbek., Alzheimer, M. Achucarro, F. H. Levy; untere Reihe von links: Frau Grombach, U. Cerletti, unbek., F. Bonfiglio, G. Perusini

Mild Cognitive Impairment (MCI)

- Typically noted in old age (above age 70 or so)
- The gray zone between normal aging and dementia.
- Forgetfulness for recent events and future engagements
- Impaired memory domain for age, sex and education level

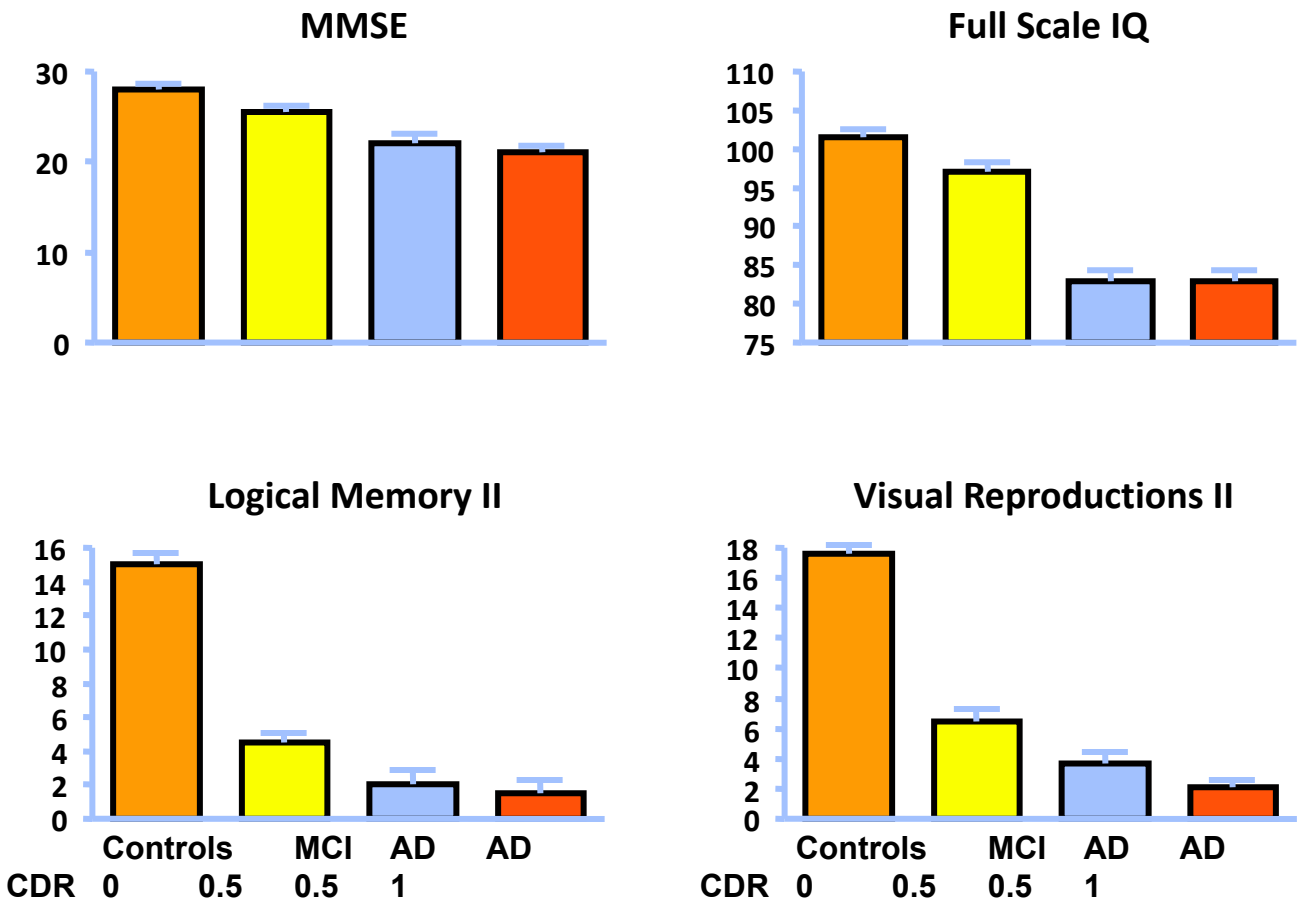


Cognitive continuum

Normal

Mild Cognitive Impairment

Alzheimer's Dementia


MMSE
30
20
10
0
Full Scale IQ
110
105
100
95
90
85
80
75
Logical Memory II
16
14
12
10
8
6
4
2
0
Controls
MCI
AD
AD
CDR
0
0.5
0.5
1
Visual Reproductions II
18
16
14
12
10
8
6
4
2
0
Controls
MCI
AD
AD
CDR
0
0.5
0.5
1

Volumetric MRI in MCI and Alzheimer's Disease

70 y/o NORMAL **72 y/o MCI** **74 y/o AD**

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Research agenda of the field of aging and dementia

- 1980s: Mainly preoccupied with the investigation of dementia (DSM-III-R, NINDS criteria)
- 1990s: Field increasingly preoccupied with identification of high risk states for dementia
- Recently: Emphasis on identification of presymptomatic phase of neurodegenerative disease such as AD *(Dubois 2004; International expert group 2007; Alzheimer's Association and National Institute on Aging 2011)*
- Various terms were used to describe the grey zone between normal aging and dementia

Mild Cognitive Impairment Criteria

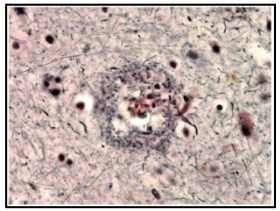
- Cognitive / Memory Complaint
- Normal General Cognitive Function
- Normal Activities of Daily Living
- Memory or other Cognitive Domains Impaired for Age and Education
- Not Demented

(Petersen RC, 1999, 2004)

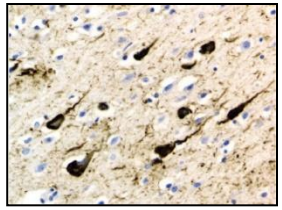
Alzheimer's Disease - Neuropathology

Classic features of AD

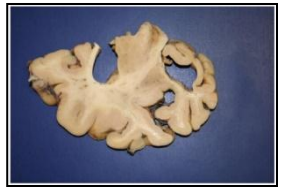
- **Neuritic plaques**
  - Extracellular deposits of a beta-amyloid protein fragments



- **Neurofibrillary tangles**
  - Intracellular fibers of tau protein



- **Subsequent neurodegeneration**
  - Accumulation of cell injury/ death and neuronal loss
  - Atrophy starts in the entorhinal cortex and hippocampus



Farlow, MR. (2007). Pictures: Courtesy of Dr. B Ghetti

Presymptomatic Alzheimer's Disease – Current research agenda of the field

- The National Institute on Aging (NIA) and Alzheimer's Association (AA) expert panel has called for characterization and understanding of the presymptomatic phase of Alzheimer's disease (AD)
- In the past, we had to wait until the patient dies to investigate plaques and tangles
  - Amyloid imaging using various ligands (e.g., PiB-PET)
  - Recently, tau imaging was developed
  - Markers of neurodegeneration:
    - Cortical thickness as measured by brain MRI
    - Synaptic loss as measured by FDG-PET

NIA-AA Criteria: Diagnosis of MCI due to AD

Clinical Research Criteria intended to be used only in research settings

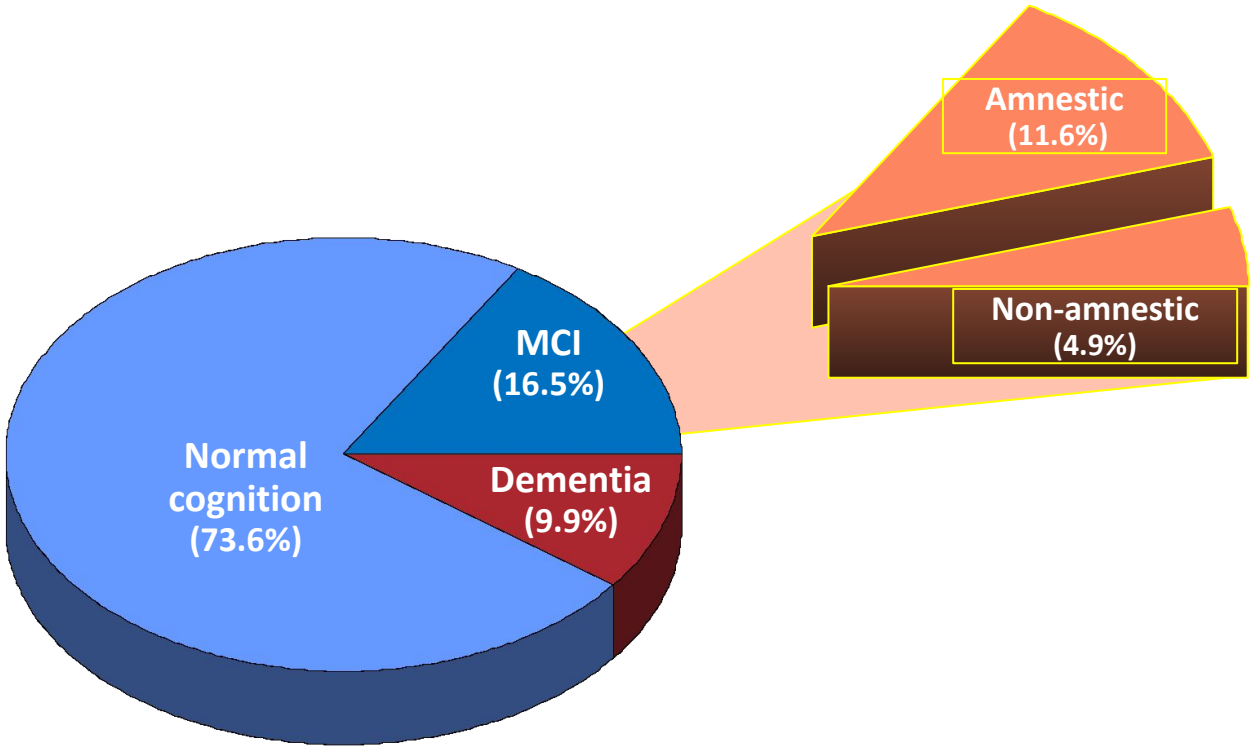
Table 3
MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI–core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

Albert et al., Alzheimer's Dement. 2011 May;7(3):270-9.

Population-Based Prevalence of MCI and Dementia

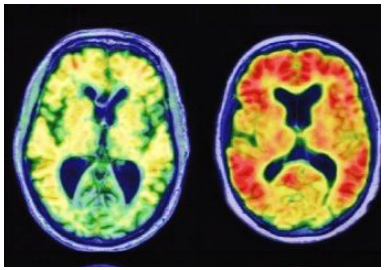


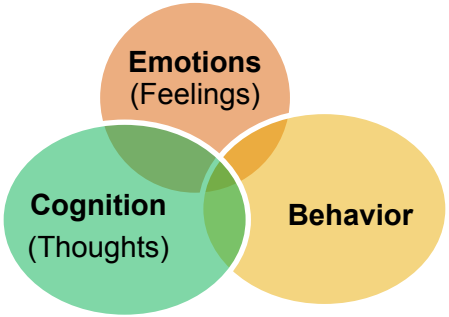
Estimates of MCI and dementia are age- and sex-adjusted to the Olmsted County, MN, population

Geda Research Team

Overarching aim: To investigate the biobehavioral aspects of brain aging, presymptomatic Alzheimer's Disease (AD) and mild cognitive impairment (MCI) in ethnically and geographically diverse samples.

- Lifestyle factors (e.g., physical exercise, mentally stimulating activities) and brain aging
- Neuropsychiatric symptoms, neuroimaging biomarkers and brain aging
- Behavioral interventions, emotion and cognition





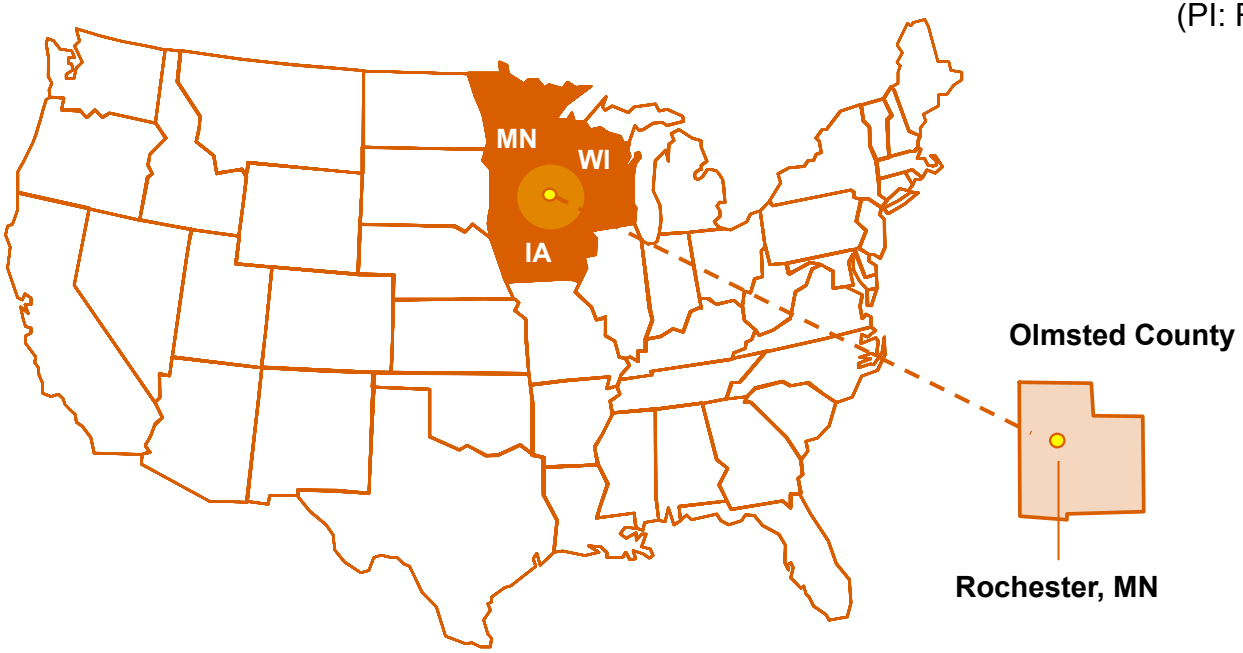
Themes of research

- Lifestyle factors (mentally stimulating activities, physical activity) and their association with the risk of incident MCI or incident dementia.
- Behavioral predictors (apathy, agitation, irritability and depression) and their association with the risk of incident MCI or incident dementia.

Study setting

Population-based *Mayo Clinic Study of Aging* in Olmsted County, Minnesota, USA

(PI: Ronald C. Petersen, MD, PhD)

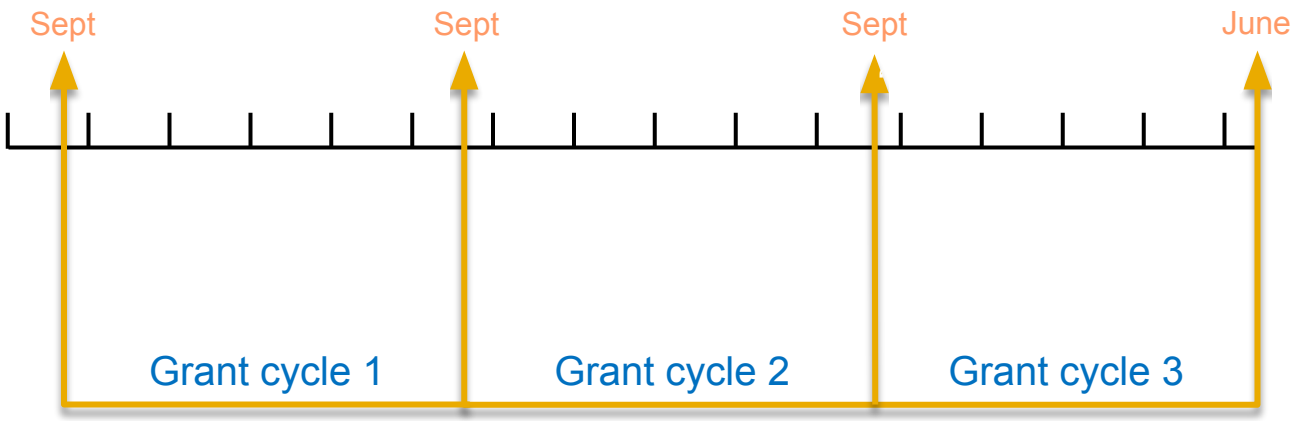


Roberts et al., 2008

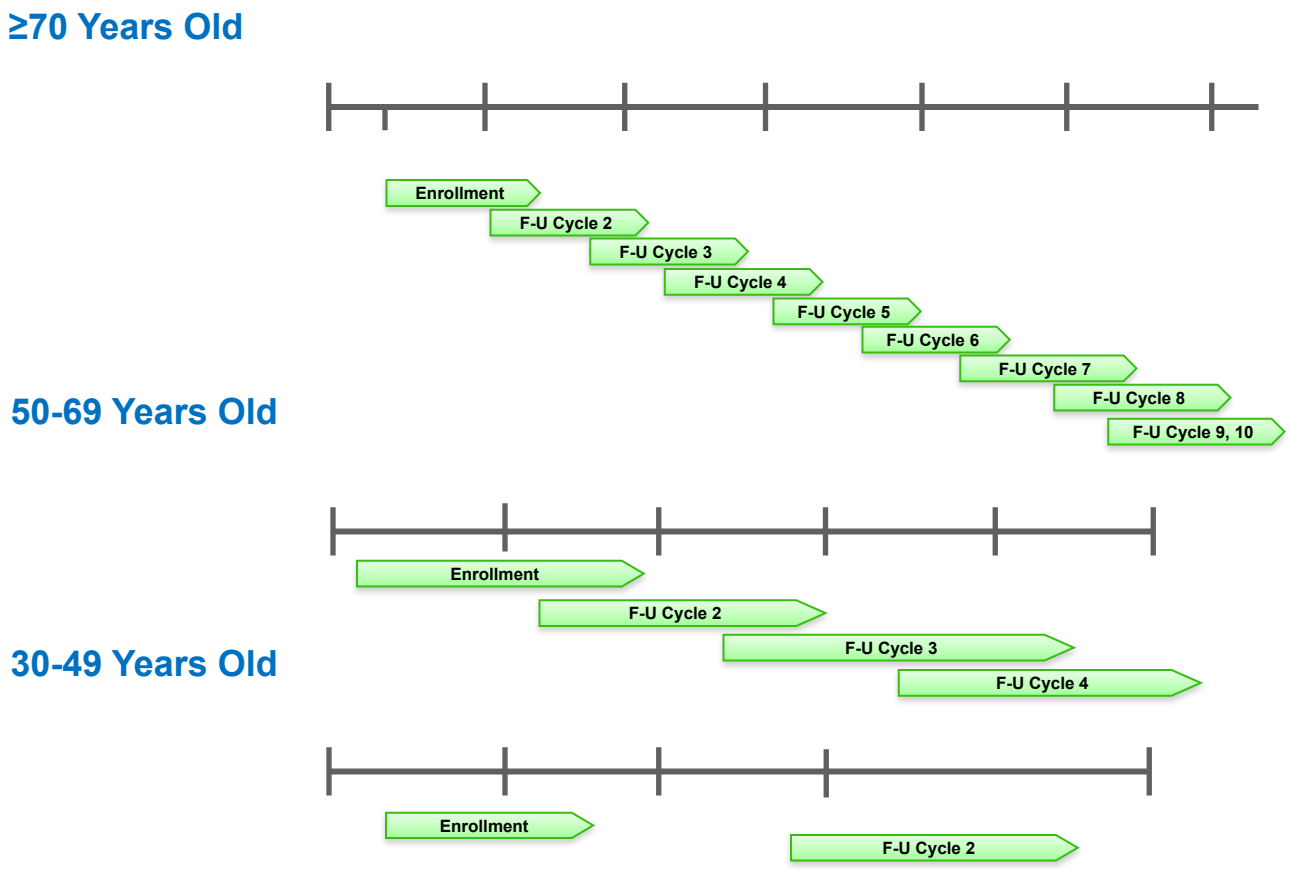
Mayo Olmsted Study of Aging

Population-based study of 5000+
(3200 active) nondemented persons age
30-89 years in Olmsted County, MN

Mayo Olmsted Study of Aging



Cycles of recruitment and follow-up



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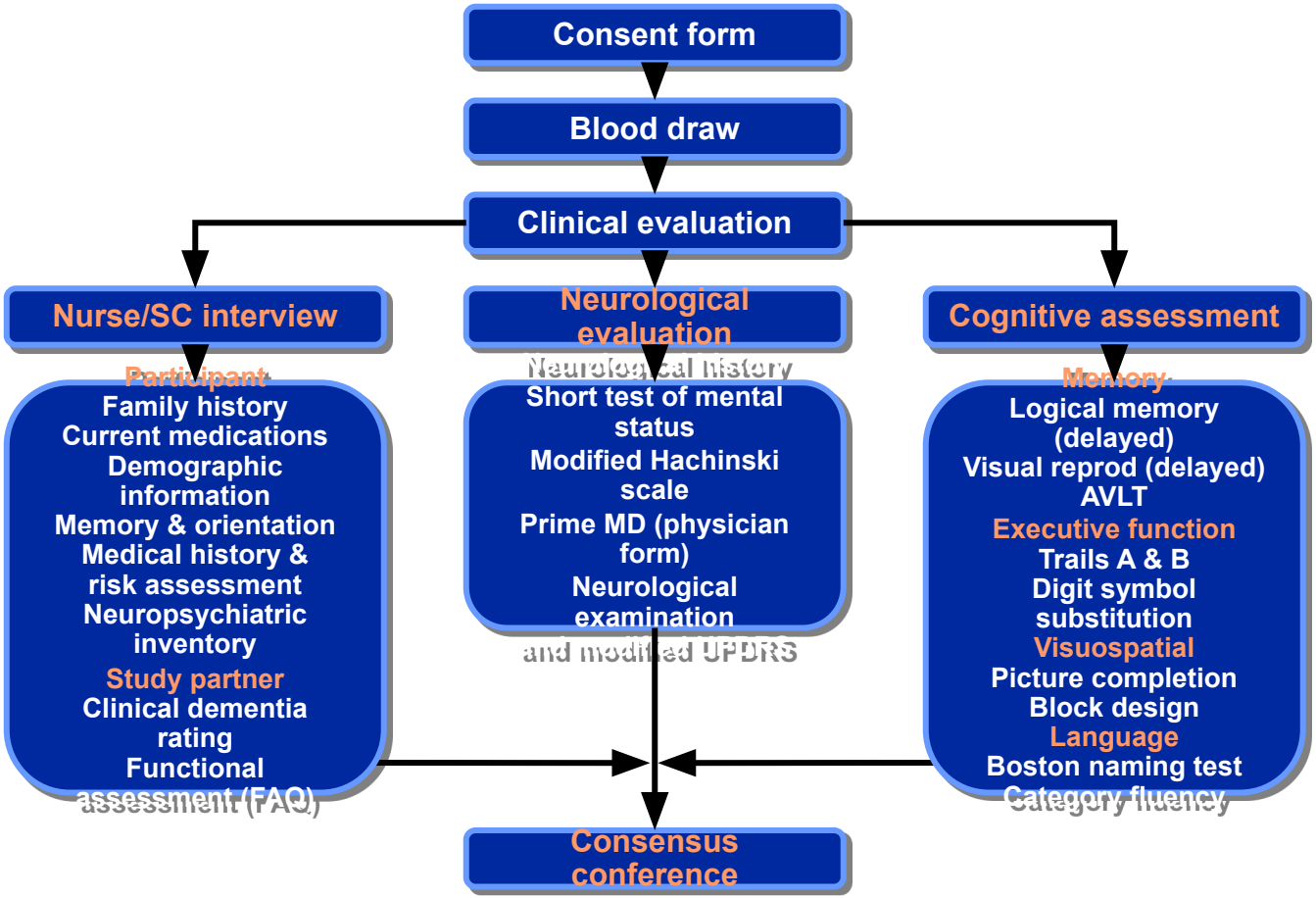
Evaluation


Consent form
Blood draw
Clinical evaluation
Nurse/SC interview
Participant
Family history
Current medications
Demographic information
Memory & orientation
Medical history & risk assessment
Neuropsychiatric inventory
Study partner
Clinical dementia rating
Functional assessment (FAQ)
Neurological evaluation
Neurological history
Short test of mental status
Modified Hachinski scale
Prime MD (physician form)
Neurological examination
and modified UPDRS
Cognitive assessment
Memory
Logical memory (delayed)
Visual reprod (delayed)
AVLT
Executive function
Trails A & B
Digit symbol substitution
Visuospatial
Picture completion
Block design
Language
Boston naming test
Category fluency
Consensus conference

Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the APOE ε4 Genotype

Krell-Roesch J, Vemuri P, Pink A, Roberts RO, Stokin GB, Mielke MM, Christianson TJ, Knopman DS, Petersen RC, Kremers WK, Geda YE.

JAMA Neurol. 2017 Mar 1;74(3):332-338. doi: 10.1001/jamaneurol.2016.3822.

The 2nd most talked about paper of the year in 2017 for JAMA Neurology

Research question: Mental activity

"I am 80 years old. If I am mentally active (e.g., computer use), will it reduce my risk of MCI?"

ARTICLE OPEN ACCESS

Quantity and quality of mental activities and the risk of incident mild cognitive impairment

Janina Krell-Roesch, PhD, Jeremy A. Syrjanen, MSc, Maria Vassilaki, MD, PhD, MPH, Mary M. Machulda, PhD, Michelle M. Mielke, PhD, David S. Knopman, MD, Walter K. Kremers, PhD, Ronald C. Petersen, MD, PhD, and Yonas E. Geda, MD, MSc

Correspondence
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Neurology® 2019;93:e548-e558. doi:10.1212/WNL.0000000000007897

Abstract

Objective
To investigate whether timing, number, and frequency of mentally stimulating activities in midlife and late life are associated with the risk of incident mild cognitive impairment (MCI).

Methods
We conducted a prospective cohort study in the setting of the population-based Mayo Clinic Study of Aging in Olmsted County, Minnesota, including 2,000 individuals aged ≥70 years who were cognitively unimpaired at baseline and were followed for a median of 5.0 years. Participants completed a self-reported survey on timing, number, and frequency of engagement in 5 mentally stimulating activities (reading books, computer use, social activities, playing games, craft activities) at baseline.

Results
The risk of incident MCI was significantly reduced for participants who engaged in social activities (hazard ratio [95% confidence interval] 0.80 [0.64–0.99]) and playing games (0.80 [0.66–0.98]) in both late life and midlife combined. Using a computer was associated with a decreased risk regardless of timing (not late life but midlife: 0.52 [0.31–0.88]; late life but not midlife: 0.70 [0.56–0.88]; late life and midlife: 0.63 [0.51–0.79]). Craft activities were associated with a reduced risk of incident MCI only when carried out in late life but not midlife (0.58 [0.34–0.97]). Furthermore, engaging in a higher number of activities in late life was associated with a significantly reduced risk of incident MCI (any 2 activities: 0.72 [0.53–0.99], any 3: 0.55 [0.40–0.77], any 4: 0.44 [0.30–0.65], all 5: 0.57 [0.34–0.96]).

Conclusion
Engaging in a higher number of mentally stimulating activities, particularly in late life, is associated with a decreased risk of MCI among community-dwelling older persons.

RELATED ARTICLE

Editorial
Frequency, number, and timing of mental activity and risk of mild cognitive impairment
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Dignity Health.

JAMA Neurology | Original Investigation

Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the *APOE* ε4 Genotype

Janina Krell-Roesch, PhD; Prashanthi Vemuri, PhD; Anna Pink, MD; Rosebud O. Roberts, MBChB, MS; Gorazd B. Stokin, MD, PhD; Michelle M. Mielke, PhD; Teresa J. H. Christianson, BS; David S. Knopman, MD; Ronald C. Petersen, MD, PhD; Walter K. Kremers, PhD; Yonas E. Geda, MD, MSc

IMPORTANCE Cross-sectional associations between engagement in mentally stimulating activities and decreased odds of having mild cognitive impairment (MCI) or Alzheimer disease have been reported. However, little is known about the longitudinal outcome of incident MCI as predicted by late-life (aged ≥70 years) mentally stimulating activities.

OBJECTIVES To test the hypothesis of an association between mentally stimulating activities in late life and the risk of incident MCI and to evaluate the influence of the apolipoprotein E (*APOE*) ε4 genotype.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a prospective, population-based cohort study of participants in the Mayo Clinic Study of Aging in Olmsted County, Minnesota. Participants 70 years or older who were cognitively normal at baseline were followed up to the outcome of incident MCI. The study dates were April 2006 to June 2016.

MAIN OUTCOMES AND MEASURES At baseline, participants provided information about mentally stimulating activities within 1 year before enrollment into the study. Neurocognitive assessment was conducted at baseline, with evaluations at 15-month intervals. Cognitive diagnosis was made by an expert consensus panel based on published criteria. Hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazards regression models after adjusting for sex, age, and educational level.

RESULTS The final cohort consisted of 1929 cognitively normal persons (median age at baseline, 77 years [interquartile range, 74-82 years]; 50.4% [n = 973] female) who were followed up to the outcome of incident MCI. During a median follow-up period of 4.0 years, it was observed that playing games (HR, 0.78; 95% CI, 0.65-0.95) and engaging in craft activities (HR, 0.72; 95% CI, 0.57-0.90), computer use (HR, 0.70; 95% CI, 0.57-0.85), and social activities (HR, 0.77; 95% CI, 0.63-0.94) were associated with a decreased risk of incident MCI. In a stratified analysis by *APOE* ε4 carrier status, the data point toward the

Author Video Interv
JAMA Report Videc

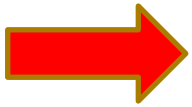
Supplemental cont

JAMA Neurology

The Most Talked About Articles of 2017

These are the top articles published in *JAMA Neurology* in 2017 as measured by Altmetric, which provides a quantitative measure of the attention each scholarly article receives in traditional and social media.

Click the article links to read the articles or the donuts to learn more about the article's Altmetric performance.



1158 **Association of Playing High School Football With Cognition and Mental Health Later in Life**

672 **Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the *APOE* ε4 Genotype**

580 **Trends in Dementia Incidence in a Birth Cohort Analysis of the Einstein Aging Study**

490 **Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE)**

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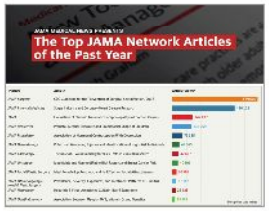


Background

- Mentally stimulating* activities are associated with decreased risk of cognitive decline *(Vemuri et al., 2014)* and dementia *(Wilson et al., 2002; Fratiglioni et al., 2004; Then et al., 2013)*
- Cognitive activities are associated with a decreased risk of amnestic MCI *(Verghese et al., 2006)* and vascular cognitive impairment *(Verghese et al., 2009)* in a convenience sample of community-dwelling elderly
- We have reported a cross-sectional association between mentally stimulating activities and decreased odds of having MCI *(Geda et al., 2011)*
- * Interchangeably used terms: cognitively stimulating activities, intellectually stimulating activities

Objective

- To investigate the association between mentally stimulating activities in late life and the risk of incident MCI

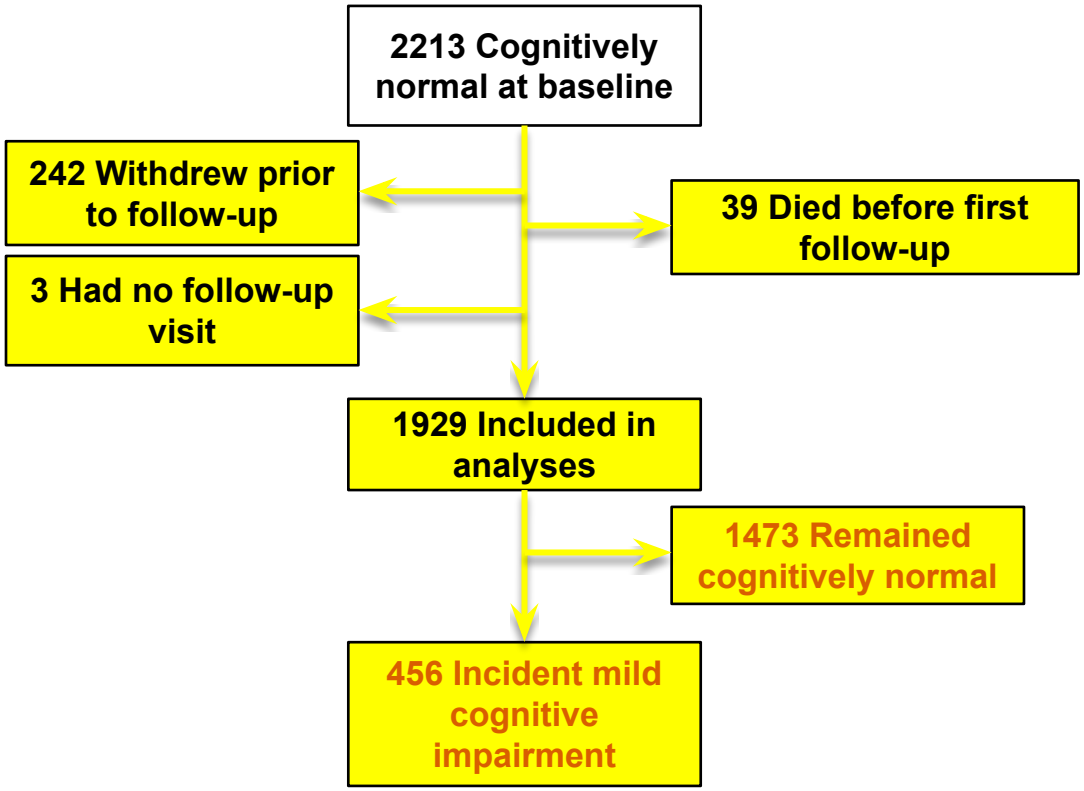
- Exposures of interest (determined based on cross-sectional study)
  - - Reading books
  - - Craft activities (e.g., knitting, pottery, woodworking)
  - - Computer activities
  - - Playing games (e.g., playing cards, crossword puzzles)
  - - Social activities (e.g., going out to movies and theaters)

- To additionally evaluate the impact of APOE ε4 genotype, a well-known risk factor for MCI and dementia

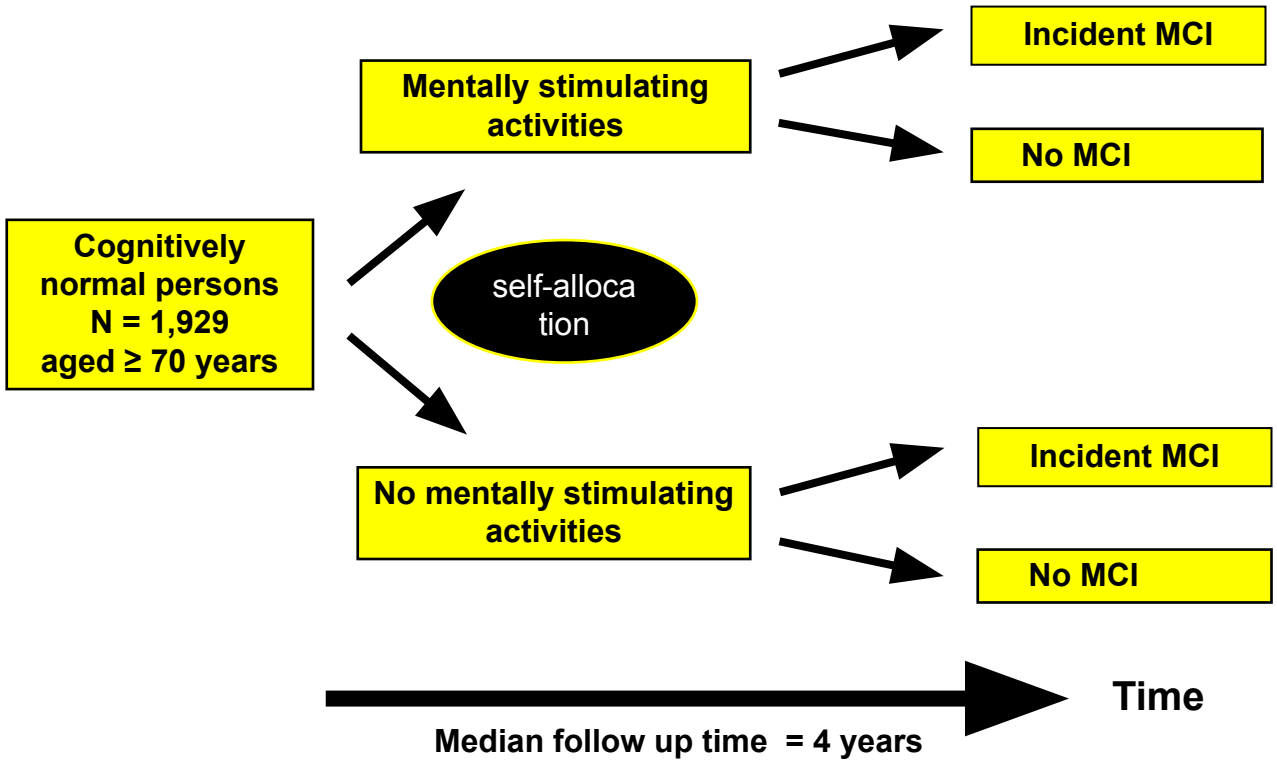
Methods

- Engaging in mentally stimulating activities in the year prior to study participation
  - Assessed using a structured survey with ordinal responses (Frequency: once a month or less, 2-3 times a month, 1-2 times per week, 3-4 times per week, 5-6 times per week, daily)
  - Operational definition: Frequency at least 1-2 times per week
- Outcome of incident MCI measured by expert consensus panel
  - - Based on published criteria (Petersen et al., 1999; Petersen et al., 2004; Winblad et al., 2004), after reviewing neurological, psychometric and other pertinent data

Flow Chart


2213 Cognitively normal at baseline
242 Withdrew prior to follow-up
39 Died before first follow-up
3 Had no follow-up visit
1929 Included in analyses
1473 Remained cognitively normal
456 Incident mild cognitive impairment

Study Design



Statistical Analysis

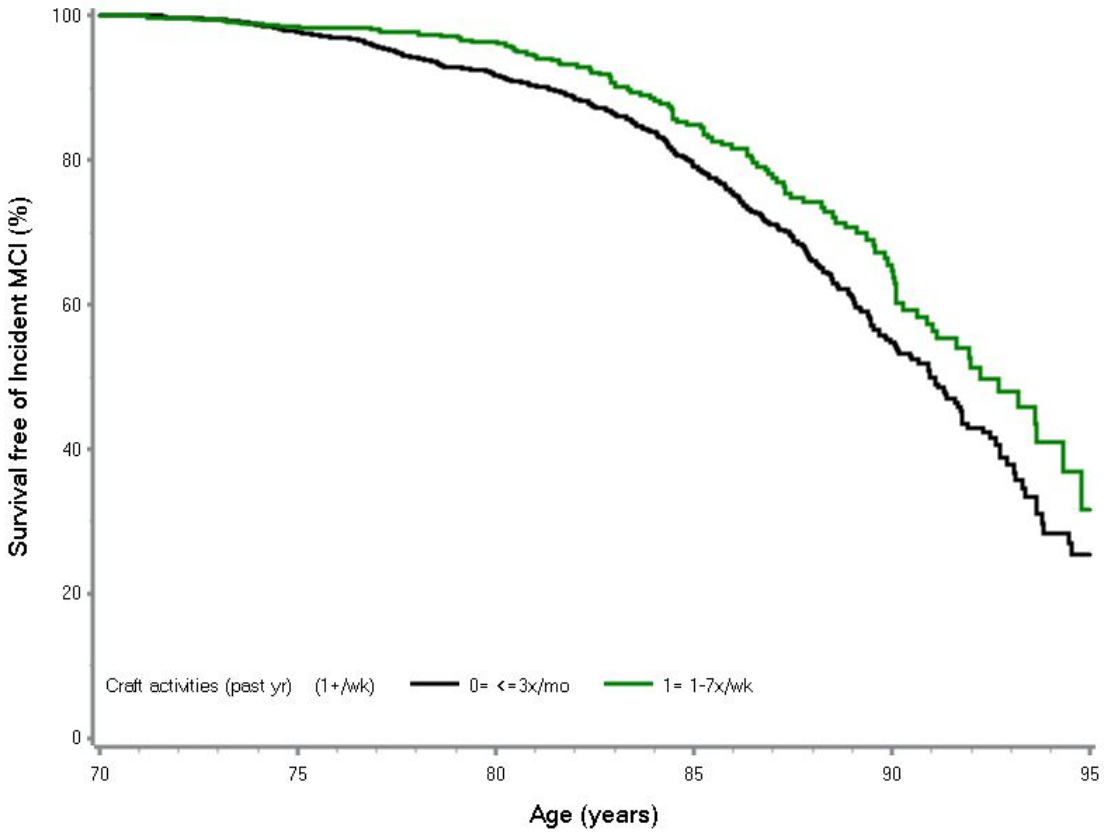
- Risk of incident MCI was estimated by using hazard ratios (HR) and 95% confidence intervals (95% CI)
  - Calculated from Cox proportional hazards model after adjusting for age (as a time scale. Therneau T 2000), sex, education and medical comorbidity
- Additional stratified analyses by APOE ε4 genotype

Risk of incident MCI as predicted by mentally stimulating activities

Variable	No. at Risk	No. with incident MCI	HR (95%CI)[1]	p	HR (95%CI)[2]	p
Read books	1083	240	0.83 (0.68, 1.01)	0.06	0.86 (0.71, 1.05)	0.14
Play games	1108	245	0.78 (0.65, 0.95)	0.012	0.83 (0.69, 1.01)	0.06
Craft activities	502	104	0.72 (0.57, 0.90)	0.004	0.78 (0.62, 0.98)	0.030
Computer activities	1077	193	0.70 (0.57, 0.85)	<0.001	0.74 (0.61, 0.90)	0.002
Social activities	767	154	0.77 (0.63, 0.94)	0.009	0.79 (0.64, 0.96)	0.017

[1]Model adjusted for age (scale), sex, education.
[2]Model also adjusted for medical comorbidity/ depression/ APOE ε4 status.

Kaplan Meier Survival Curve: Craft activities



Conclusion

- Cognitively normal elderly individuals who engage in specific mentally stimulating activities *even in late life* have a decreased risk of incident MCI.

- The data points towards:
  - a reduced risk of incident MCI for APOE ε4 non-carriers who engage in mentally stimulating activities
  - an increased risk of incident MCI for APOE ε4 carriers who do not engage in mentally stimulating activities

- Future research is needed to understand the mechanisms linking mentally stimulating activities and cognition in late life

Timing of Physical Activity, Apolipoprotein E ε4 Genotype, and Risk of Incident Mild Cognitive Impairment

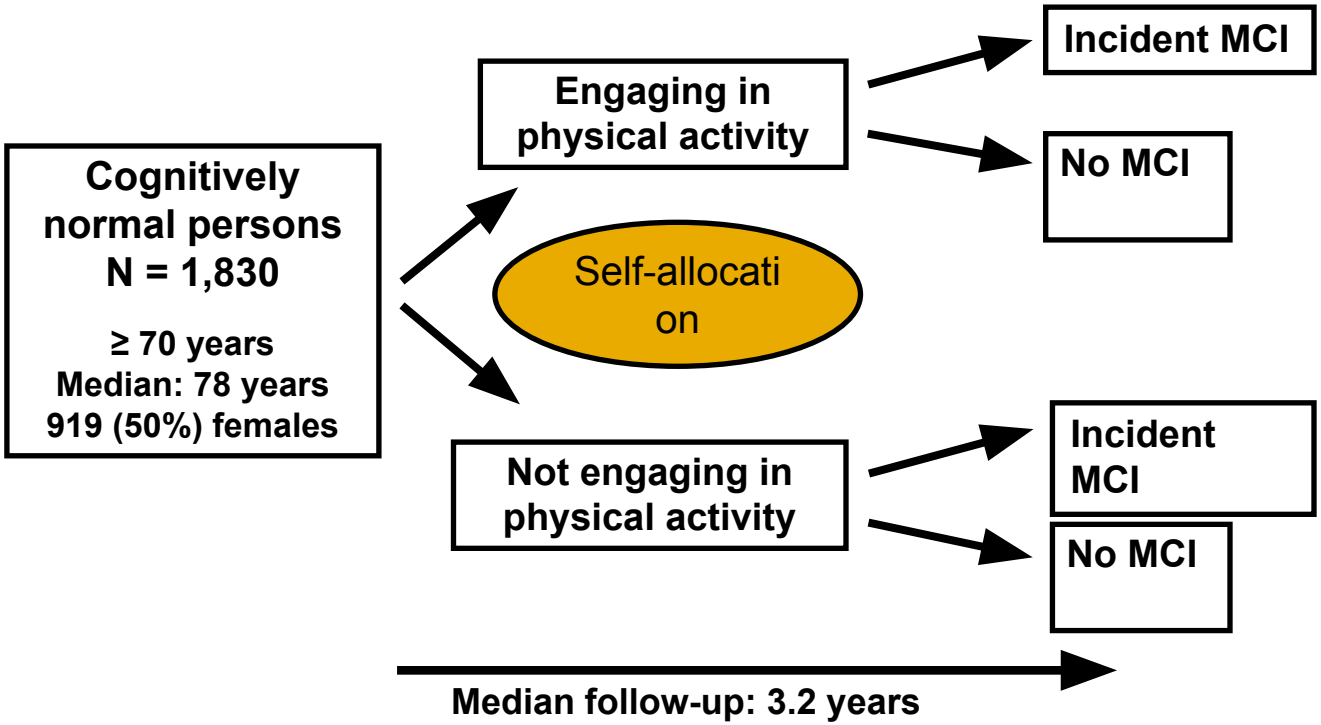
Krell-Roesch J, Pink A, Roberts RO, Stokin GB, Mielke MM, Spangehl KA, Bartley MM, Knopman DS, Christianson TJ, Petersen RC, Geda YE.

J Am Geriatr Soc. 2016 Dec;64(12):2479-2486.

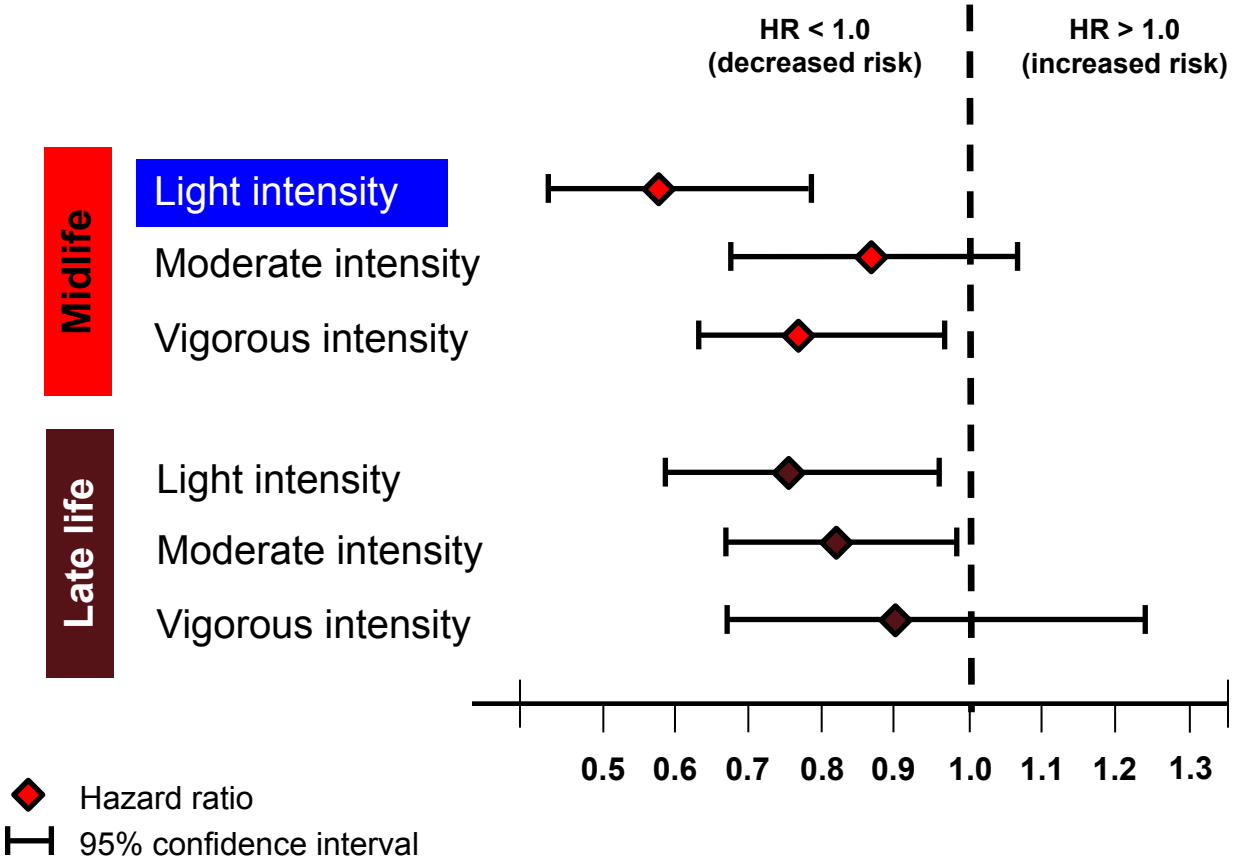
“I am 78 years old: if I start a new habit of leisurely walk about 2 to 3 times per week; does it help me reduce the risk of dementia?”

- Leisurely walk
- Observations made in Rochester, Minnesota : in summer, it is customary for elderly couples to go for a relaxed walk after a dinner.
- Typically we here about brisk walk for 30 minutes for 5 days per week : for optimal health.
- How about a simple, leisurely walk : is it any good?

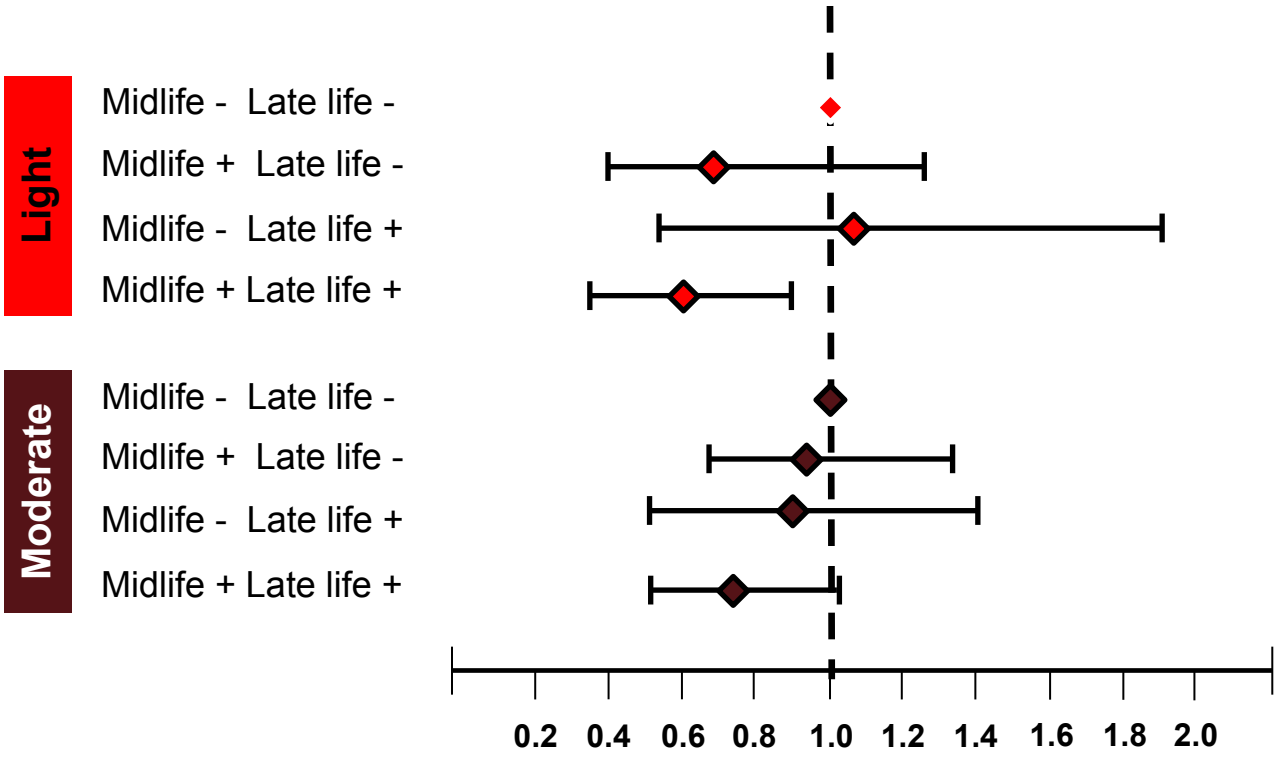
Prospective cohort study



Main results

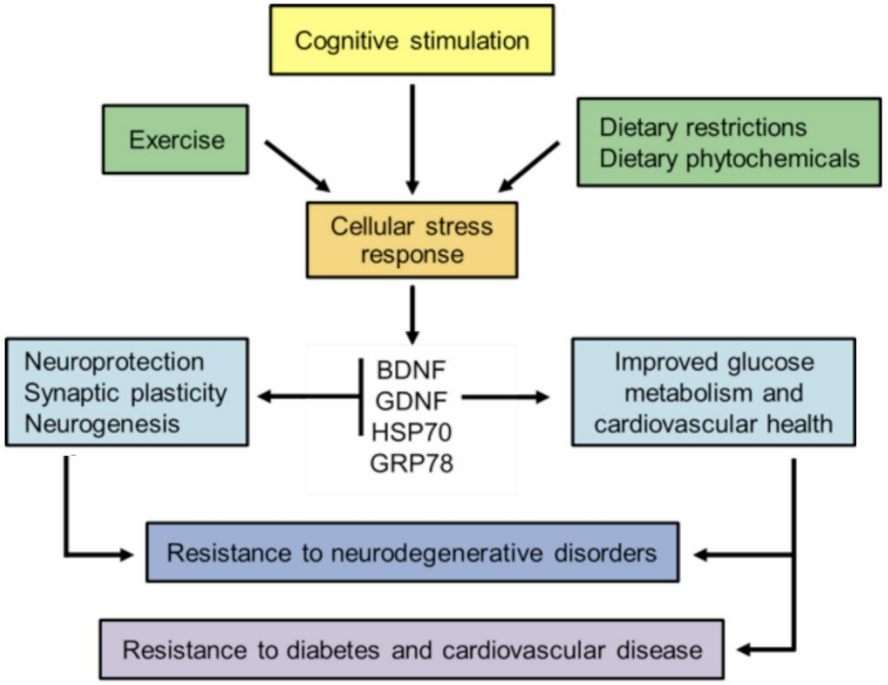


Interaction: Timing of physical activity



Mechanistic Model:

Effects of exercise, dietary restriction & cognitive stimulation on neurodegeneration



Mattson *et al. Nature Reviews Neuroscience* **2006,** 7; 278–294

Neuropsychiatric symptoms (NPS), MCI and dementia

Neuropsychiatric symptoms (NPS), MCI and dementia

- Study 1: From normal aging to incident MCI as predicted by baseline NPS *(Geda et al. Am J Psychiatry. 2014)*
- Study 2: From MCI to incident dementia as predicted by baseline NPS *(Pink et al., Neurology. 2015)*
- NPS and neuroimaging biomarkers of pre-symptomatic AD [submitted to Molecular Psychiatry]

Methods

- **Measurement of exposure of interest** : NPS at baseline measured by Neuropsychiatric Inventory Questionnaire (NPI-Q
- **Measurement of outcome of interest** **:** Classification of normal cognitive aging, MCI, and dementia
  - adjudicated by an expert consensus panel
  - based on published criteria
  - after reviewing neurologic, cognitive, and other pertinent data

- **Risk measurement** : Hazard ratios (HR) and 95% confidence intervals (95% CI) were computed using Cox proportional hazards model, with age as a time scale

Study 1: Objective

- Prospective cohort study to estimate the risk of incident mild cognitive impairment (MCI) in cognitively normal elderly (aged ≥70 years) individuals, as predicted by baseline neuropsychiatric symptoms (NPS)

Design: Prospective cohort study

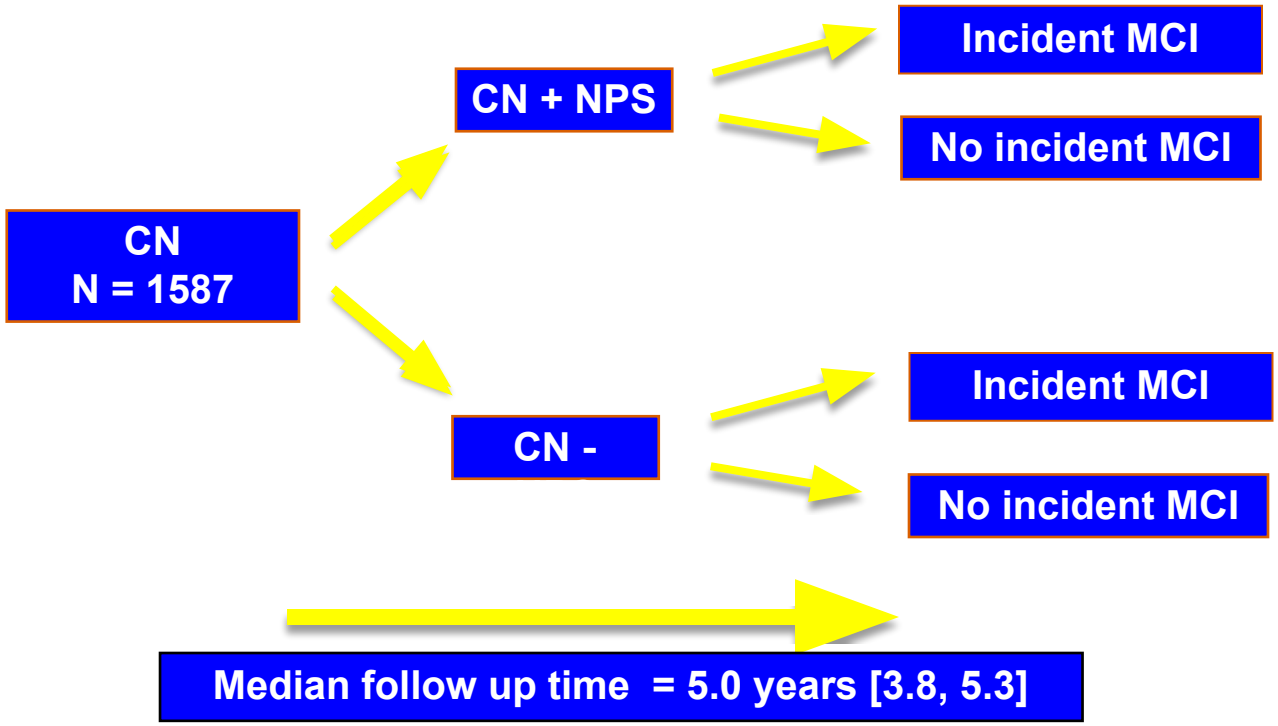


TABLE 3. Risk of Incident Mild Cognitive Impairment by Baseline Nonpsychotic Neuropsychiatric Symptoms

	Risk Adjusted for Age (Time Scale), Sex, and Education			Risk Additionally Adjusted for Medical Comorbidity		
Psychiatric Symptom	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Total mild cognitive impairment						
Depression	1.68	1.27–2.22	<0.001	1.63	1.23–2.16	<0.001
Apathy	2.46	1.63–3.70	<0.001	2.26	1.49–3.41	<0.001
Anxiety	1.91	1.31–2.78	<0.001	1.87	1.28–2.73	0.001
Agitation	3.13	1.94–5.05	<0.001	3.06	1.89–4.93	<0.001
Irritability	1.85	1.32–2.60	<0.001	1.84	1.31–2.58	<0.001
Appetite/eating	1.44	0.96–2.17	0.08	1.34	0.89–2.02	0.16
Motor disturbance	1.63	0.52–5.11	0.40	1.60	0.51–5.00	0.42
Nighttime behaviors[a]	1.48	1.05–2.08	0.03	1.46	1.03–2.06	0.03
Amnestic mild cognitive impairment						
Depression	1.75	1.23–2.48	0.002	1.74	1.22–2.47	0.002
Apathy	1.98	1.13–3.47	0.02	1.93	1.09–3.41	0.02
Anxiety	1.65	0.99–2.76	0.05	1.64	0.98–2.74	0.06
Agitation	2.18	1.07–4.44	0.03	2.16	1.06–4.41	0.03
Irritability	1.69	1.09–2.64	0.02	1.69	1.08–2.63	0.02
Appetite/eating	1.09	0.61–1.95	0.78	1.06	0.59–1.91	0.85
Motor disturbance	0.84	0.12–6.01	0.86	0.84	0.12–5.97	0.86
Nighttime behaviors[a]	1.44	0.93–2.24	0.11	1.44	0.93–2.25	0.10
Nonamnestic mild cognitive impairment						
Depression	1.26	0.68–2.31	0.46	1.18	0.64–2.16	0.60
Apathy	3.81	1.97–7.38	<0.001	3.19	1.62–6.26	<0.001
Anxiety	2.84	1.50–5.35	0.001	2.74	1.45–5.16	0.002
Agitation	5.14	2.46–10.7	<0.001	4.92	2.36–10.3	<0.001
Irritability	2.18	1.18–4.02	0.01	2.18	1.18–4.03	0.01
Appetite/eating	1.52	0.70–3.30	0.29	1.31	0.60–2.85	0.50
Motor disturbance	4.12	1.00–16.9	<0.05	3.89	0.94–16.0	0.06
Nighttime behaviors[a]	2.11	1.15–3.88	0.02	2.04	1.11–3.76	0.02

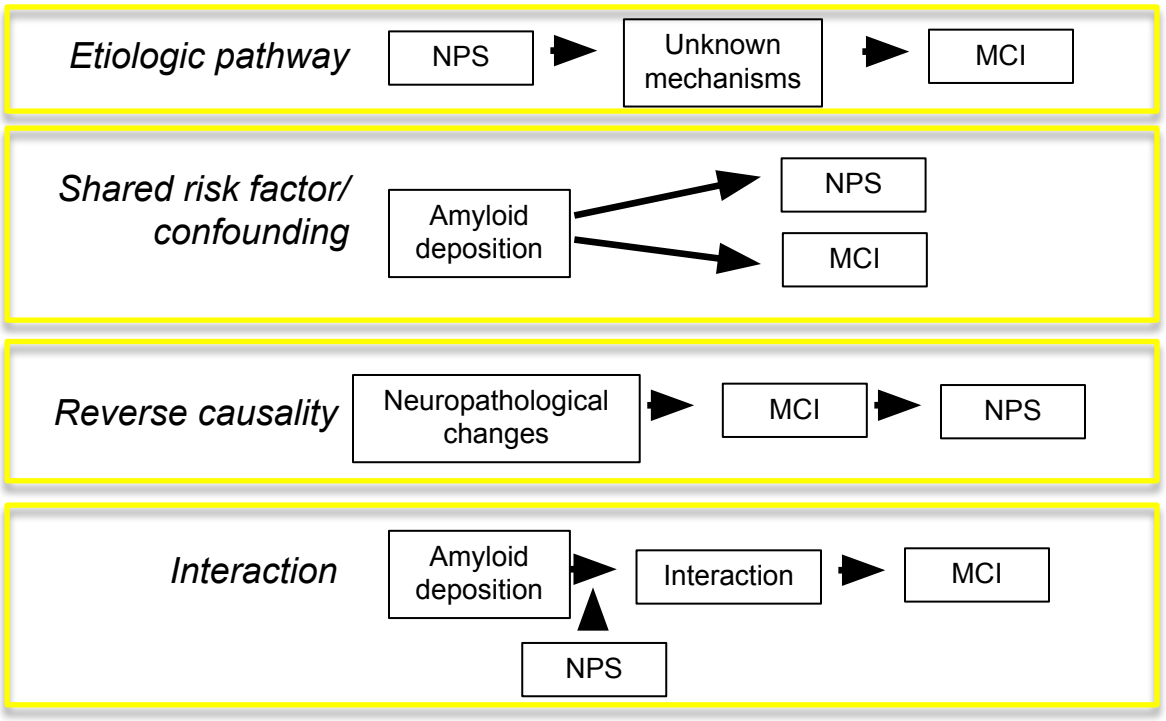
[a] Nighttime behaviors assessment data were not available for 271 participants (the informant was unable to assess).

TABLE 4. Risk of Incident Mild Cognitive Impairment by Baseline Psychotic Symptoms and Other Emotional Behaviors

	Risk Adjusted for Age (Time Scale), Sex, and Education			Risk Additionally Adjusted for Medical Comorbidity		
Psychiatric Symptom	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Total mild cognitive impairment						
Disinhibition	2.60	1.42–4.75	0.002	2.59	1.42–4.73	0.002
Euphoria	5.07	2.23–11.5	<0.001	5.10	2.24–11.6	<0.001
Delusions	0.60	0.08–4.27	0.61	0.55	0.08–3.95	0.55
Hallucinations	1.57	0.39–6.37	0.52	1.48	0.37–5.99	0.58
Amnestic mild cognitive impairment						
Disinhibition	1.49	0.55–4.01	0.43	1.48	0.55–4.00	0.44
Euphoria	2.42	0.59–9.84	0.22	2.41	0.59–9.83	0.22
Delusions	1.02	0.14–7.34	0.98	1.00	0.14–7.15	1.00
Hallucinations	1.32	0.18–9.52	0.78	1.30	0.18–9.34	0.80
Nonamnestic mild cognitive impairment						
Disinhibition	5.22	2.26–12.0	<0.001	5.18	2.24–12.0	<0.001
Euphoria	10.7	3.27–35.1	<0.001	11.3	3.44–37.2	<0.001
Delusions[a]			0.99			0.99
Hallucinations	3.10	0.42–22.7	0.27	2.76	0.38–20.3	0.32

[a] Values for hazard ratios and 95% confidence intervals were not applicable.

Potential mechanisms linking NPS with MCI/ dementia



Adapted from Geda et al., Alzheimers Dement. 2013 Sep;9(5):602-8.

NPS and neuroimaging biomarkers of presymptomatic AD

Our team has reported cross-sectional associations between

- anxiety symptoms with reduced global cortical thickness and reduced thickness of the frontal and temporal cortex as measured by MRI *(Pink et al., 2016)*
- depressive and anxiety symptoms with an abnormal FDG-PET, and the point estimate is even higher for APOE ε4 carriers *(Krell-Roesch et al., 2016)*
- depression and anxiety with an abnormal PiB-PET *(Krell-Roesch et al., in press)*

Frequency of NPS among Cognitively Unimpaired (CU) & MCI with abnormal amyloid deposition

Methods

- Population-based, cross-sectional study

N = 1627, aged ≥ 50 years, 54% males, median age 73 years

- 997 CU/A-, 446 CU/A+, 78 MCI/A-, 106 MCI/A+

Key Findings

- For most NPS, highest frequency of NPS was found in MCI/A+, and the lowest in CU/A-

- Odds ratios of having NPS, depression (BDI ≥ 13) or anxiety (BAI ≥ 8, ≥ 10) were consistently highest for MCI/A+

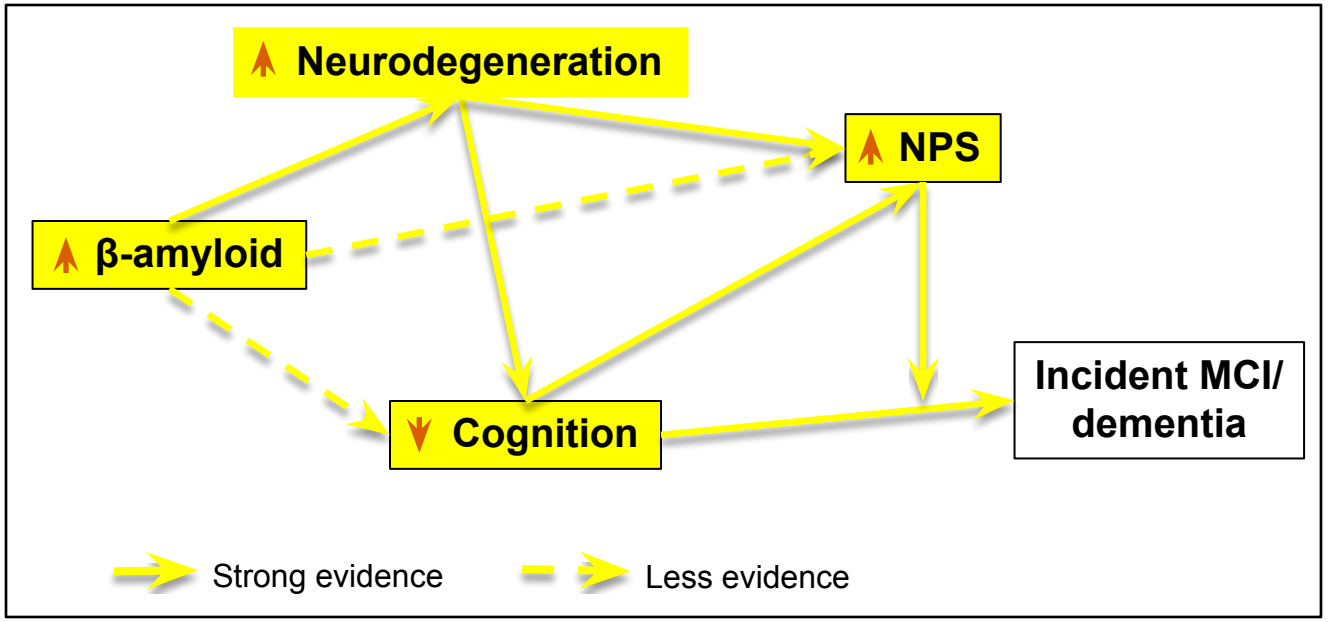
Abbreviations: CU = cognitively unimpaired; MCI = mild cognitive impairment; A- = normal PiB-PET; A+ = abnormal PiB-PET

Frequency of NPS among CU & MCI

NPS		N	OR (95% CI)	p
Depression	CU/A-	997	1.00 (reference)	
	CU/A+	446	1.13 (0.76, 1.67)	0.55
	MCI/A-	78	1.33 (0.65, 2.72)	0.43
	MCI/A+	106	3.48 (2.05, 5.90)	<0.001
Apathy	CU/A-	997	1.00 (reference)	
	CU/A+	446	1.62 (0.90, 2.91)	0.11
	MCI/A-	78	2.51 (1.03, 6.09)	0.042
	MCI/A+	106	7.06 (3.59, 13.88)	<0.001
BAI ≥ 8	CU/A-	995	1.00 (reference)	
	CU/A+	445	1.22 (0.80, 1.86)	0.35
	MCI/A-	78	2.88 (1.52, 5.44)	0.001
	MCI/A+	106	2.97 (1.66, 5.30)	<0.001

Adjusted for age, sex, education, and APOE ε4 genotype status. DV = dependent variable; IV = independent variable. OR = odds ratio; CI = confidence interval.

Theoretical model linking NPS with AD biomarkers and cognitive outcomes



Geda et al. 2017. American Journal of Geriatric Psychiatry

Insulin resistance and risk of dementia

- Following a meal : insulin spikes then it falls down to baseline in a normal person.
- Frequent feeding particularly carbohydrates (bread, pasta etc.) leads to frequent insulin spikes.
- Excess and frequent Carbohydrate consumption leads to resetting of insulin at high level even in a fasting state = Insulin resistance.
- "A dietary pattern with intake from carbohydrates is associated with increased risk of MCI or dementia in elderly persons."
  - Roberts RO, Roberts LA, Geda YE et al : J Alzheimers Dis. 2012;32(2):329-39

Insulin and cortisol are storage hormones

- The see-saw : when storage hormones go up then the catabolic hormones go down.
- Following a high carb meal : sleepiness. Why?
- Insulin producing tumor : excessive obesity.
- Cortisol producing pituitary gland : excessive obesity.
- The most potent stimulus to insulin is carbohydrate.
- What is to be done? Time restricted feeding 2 to 3 times per day. No snacks on refined sugar. Vegetables and fruit.
  - What type of fruits? It is better to get carb/sugar from fruits than from added sugar.

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