Dementia Update: Early Detection and Treatment

James E. Galvin, MD, MPH
Executive Director: Institute for Healthy Aging and Lifespan
Director: Comprehensive Center for Brain Health
Charles E. Schmidt College of Medicine
Florida Atlantic University
Objectives

• Differentiation of Healthy aging, Dementia, and Alzheimer’s disease
• Best detection of cognitive impairment in the busy office
• Effectiveness of current medications
• Anticipated new medications
• Rational for detection and treatment of dementia
What is healthy brain aging?

• The absence of cognitive decline
  • Occurs into the 10\textsuperscript{th} decade of life
  • Still carry out their activities of daily living
  • Lead a productive and happy life

• With age, it may take longer to do things or recall information, but it usually comes back

• Memory loss is not a normal part of the aging process
What is Dementia?

• A general word to describe:
  • Change in memory and thinking abilities
  • Interferes with everyday function
  • Not caused by another disease

• Not really a diagnosis

• There are over 100 different causes of dementia
Differential Diagnosis of Dementia

**Neurodegenerative Disease**
- Alzheimer’s disease
- Dementia with Lewy bodies
- Parkinson’s disease
- Frontotemporal dementia
- Huntington’s disease
- Progressive supranuclear palsy
- Corticobasal degeneration
- Creutzfeldt-Jacob disease
- Wilson’s disease

**Vascular Disease**
- Vascular dementia
- Cerebral amyloid angiopathy
- Vasculitis

**Hydrocephalus**

**Demyelinating disorders**
- Multiple sclerosis
- Leukodystrophies

**Traumatic brain injury**

**Epilepsy**

**Metabolic Disorders**
- Hepatic encephalopathy
- Hypothyroidism
- Electrolyte disorders (sodium, calcium)

**Nutritional disorders**
- B12 deficiency
- Wernicke-Korsakoff syndrome (thiamine)

**Mitochondrial disorders**

**Toxic disorders**
- Alcoholism
- Drugs
- Heavy metals

**Neoplasia**
- Primary brain tumors
- Metastatic disease
- Paraneoplastic syndromes

**Infection**
- HIV/PML
- Neurosyphilis
- Whipple’s disease
What is Alzheimer’s Disease (AD)?

- Most common cause of dementia
- 5.4 million Americans have AD
  - 250,000 age <65 years (early-onset)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Proportion</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-74</td>
<td>2%</td>
<td>300,000</td>
</tr>
<tr>
<td>75-84</td>
<td>19%</td>
<td>2,400,000</td>
</tr>
<tr>
<td>≥85</td>
<td>42%</td>
<td>2,200,000</td>
</tr>
</tbody>
</table>

- Annual treatment costs > $200 billion
  - Costs increase as disease progresses
  - 3rd most expensive disease after cardiovascular and cancer
- Sixth leading cause of death in the US (over age 70)
- Makes up 50% of all nursing home beds
  - Median cost (2013) = $84,000
Forecast of Alzheimer’s Disease Prevalence

- 2009: 5.2 Million (est)
- 2030: 7.7 Million (est)
- 2050: 16.0 Million (est)

Prevalence of AD by Race, Ethnicity and Gender

- Risk of AD in African-Americans and Hispanics is 1.5-2 times greater than Whites
- Risk in women is 1.5 times greater than men
- May be due to other medical conditions (hypertension, diabetes, obesity)
Mixed pathology is most common cause of the clinical picture of AD.

AD: Alzheimer disease
I: Vascular disease
LB: Lewy body disease
The AD8

<table>
<thead>
<tr>
<th>Problem Description</th>
<th>YES, A change</th>
<th>NO, No change</th>
<th>N/A, Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems with judgment (e.g. falls for scams, bad financial decisions, buys gifts inappropriate for recipients)</td>
<td></td>
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<tr>
<td>Reduced interest in hobbies/activities</td>
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<td>Repeats questions, stories or statements</td>
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<td>Trouble learning how to use a tool, appliance or gadget (e.g. VCR, computer, microwave, remote control)</td>
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<tr>
<td>Forgets correct month or year</td>
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<tr>
<td>Difficulty handling complicated financial affairs (e.g. balancing checkbook, income taxes, paying bills)</td>
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<tr>
<td>Difficulty remembering appointments</td>
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</tr>
<tr>
<td>Daily problems with thinking and/or memory</td>
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</tbody>
</table>

**TOTAL AD8 SCORE**

- Remember, “Yes, a change” indicates that you think there has been a change in the last several years cause by cognitive (thinking and memory) problems
- Report cognitive loss in comparison with patient’s premorbid function
- Report interference with usual daily activities
- Consistent change, even when patient’s brief test performance is “normal”, may detect earliest symptomatic stages of dementia
- Less biased by race, culture, education or SES
- Dependent on a reliable, observant informant

Galvin JE et al, Neurology, 2005
### Memory and Recall

1. **No obvious memory loss or slight inconsistent forgetfulness that does not interfere with everyday function**

2. **Consistent mild forgetfulness or partial recollection of events that may interfere with performing everyday activities; repeats questions/statements, misplaces items, forgets appointments**

3. **Mild to moderate memory loss; more noticeable for recent events; interferes with performing everyday activities**

4. **Moderate to severe memory loss; only highly learned information remembered; new information rapidly forgotten**

5. **Severe memory loss, almost impossible to recall new information; long-term memory may be affected**

### Mood

1. **No changes in mood, interest or motivation level**

2. **Occasional sadness, depression, anxiety, nervousness or loss of interest/motivation**

3. **Daily mild issues with sadness, depression, anxiety, nervousness or loss of interest/motivation**

4. **Severe issues with sadness, depression, anxiety, nervousness or loss of interest/motivation**

### Attention and Concentration

1. **Normal attention, concentration and interaction with his/her environment and surroundings**

2. **Mild problems with attention, concentration, and interaction with environment and surroundings, may appear drowsy during day**

3. **Moderate problems with attention and concentration, may have staring spells or spend time with eyes closed, increased daytime sleepiness**

4. **Significant portion of the day is spent sleeping, not paying attention to environment, when having a conversation may say things that are illogical or not consistent with topic**

5. **Limited to no ability to pay attention to external environment or surroundings**

### Quick Dementia Rating Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Normal</td>
</tr>
<tr>
<td>2-5</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>6-12</td>
<td>Mild dementia</td>
</tr>
<tr>
<td>13-20</td>
<td>Moderate dementia</td>
</tr>
<tr>
<td>20-30</td>
<td>Severe dementia</td>
</tr>
</tbody>
</table>

**Legend:**
- **1** Mild but definite impairment in home and hobby function; more difficult chores or tasks abandoned; more complicated hobbies and interests given up
- **2** Only simple chores preserved, very restricted interest in hobbies which are poorly maintained
- **3** No meaningful function in household chores or with prior hobbies
- **4** Limited to no ability to pay attention to external environment or surroundings

**Notes:**
- **CGNITVE SUBTOTAL (QUESTIONS 1, 2, 3, 1)**
- **BEHAVIORAL SUBTOTAL (QUESTIONS 4, 5, 6, 7, 8, 10)**
- **TOTAL GEKS SCORE**
# Lewy Body Composite Risk Score

Please rate the following symptoms as being present or absent for at least 3 times over the past 6 months. Does the patient...

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?</td>
<td></td>
</tr>
<tr>
<td>Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?</td>
<td></td>
</tr>
<tr>
<td>Have a loss of postural stability (balance) with or without frequent falls?</td>
<td></td>
</tr>
<tr>
<td>Have a tremor at rest in any of the 4 extremities or head?</td>
<td></td>
</tr>
<tr>
<td>Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?</td>
<td></td>
</tr>
<tr>
<td>Have episodes of illogical thinking or incoherent, random thoughts?</td>
<td></td>
</tr>
<tr>
<td>Have frequent staring spells or periods of blank looks?</td>
<td></td>
</tr>
<tr>
<td>Have visual hallucinations (see things not really there)?</td>
<td></td>
</tr>
<tr>
<td>Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?</td>
<td></td>
</tr>
<tr>
<td>Have orthostatic hypotension or other signs of autonomic insufficiency?</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE**

Copyright 2015 *The Lewy Body Composite Risk Score* James E. Galvin
# Number-Symbol Coding Test

**KEY**

<table>
<thead>
<tr>
<th>Number</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>△</td>
</tr>
<tr>
<td>2</td>
<td>✖</td>
</tr>
<tr>
<td>3</td>
<td>−</td>
</tr>
<tr>
<td>4</td>
<td>⊥</td>
</tr>
<tr>
<td>5</td>
<td>◊</td>
</tr>
<tr>
<td>6</td>
<td>&lt;</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>⊗</td>
</tr>
<tr>
<td>9</td>
<td>∧</td>
</tr>
<tr>
<td>0</td>
<td>=</td>
</tr>
</tbody>
</table>

**SCORE**

<table>
<thead>
<tr>
<th>Practice #1</th>
<th>Practice #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 1 0 9 4</td>
<td>4 1 9 8 4 2 9 3 5 4</td>
</tr>
</tbody>
</table>

| 8 6 5 2 7 0 1 5 6 8 9 0 4 |
| ∧ ⊥ − + X < ∧ |

| 7 1 0 6 2 4 0 0 3 |
| + = ◊ < ◊ − △ + − ⊗ ⊥ |

| 1 0 3 7 9 1 5 0 5 1 0 9 3 |
| − ◊ < − ◊ ✖ + |
Modeling Neurodegenerative Diseases

A: AD vs. Controls

B: PD vs. PDD vs. Controls

C: AD vs. DLB

D: Evolution of PD-MCI
AD Treatment Targets

Amyloid Precursor Protein

Amyloid β monomer

Amyloid β oligomers

Amyloid Plaques
- NFTs (tau)
- Inflammation
- Oxidative stress

Neuronal loss, neurotransmitter loss, cognitive deficit

Secretase Inhibitors
- Selective Aβ lowering agents

Anti-aggregation
- Anti-fibril

Passive Immunization

Active Immunization

Antioxidants
- Anti-inflammatory agents
- Anti-tau aggregation/phosphorylation

Symptomatic Drugs
- Anti-cholinesterases; NMDA antagonist
Combination Therapy in Moderate-to-Severe AD


Cognition (SIB)

Function (ADCS-ADL$_{19}$)
Combination Therapy: Long Term Effects

**Predicted Mean Cognition Score**

<table>
<thead>
<tr>
<th>Years</th>
<th>No treatment</th>
<th>ChEI alone</th>
<th>COMBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80.0</td>
<td>69.0</td>
<td>70.0</td>
</tr>
<tr>
<td>2</td>
<td>70.0</td>
<td>59.0</td>
<td>60.0</td>
</tr>
<tr>
<td>3</td>
<td>60.0</td>
<td>49.0</td>
<td>50.0</td>
</tr>
<tr>
<td>4</td>
<td>50.0</td>
<td>39.0</td>
<td>40.0</td>
</tr>
</tbody>
</table>

**Predicted Mean Level of Dependence**

<table>
<thead>
<tr>
<th>Years</th>
<th>No treatment</th>
<th>ChEI alone</th>
<th>COMBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30.0</td>
<td>19.0</td>
<td>30.0</td>
</tr>
<tr>
<td>2</td>
<td>20.0</td>
<td>11.0</td>
<td>20.0</td>
</tr>
<tr>
<td>3</td>
<td>10.0</td>
<td>0.0</td>
<td>10.0</td>
</tr>
<tr>
<td>4</td>
<td>0.0</td>
<td>-1.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Cohen's d**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChEI alone vs no treatment</td>
<td>0.47***</td>
<td>0.39**</td>
<td>0.32**</td>
<td>0.23*</td>
</tr>
<tr>
<td>COMBO vs no treatment</td>
<td>0.56***</td>
<td>0.73***</td>
<td>0.76***</td>
<td>0.77***</td>
</tr>
<tr>
<td>COMBO vs ChEI alone</td>
<td>0.10</td>
<td>0.34**</td>
<td>0.44***</td>
<td>0.49***</td>
</tr>
</tbody>
</table>
Current Phase II/III Trials

- 1469 Studies currently active
- 450 Studies currently enrolling

New Drugs
- Amyloid: β and γ secretase inhibitors, clearance mechanisms
- Tau
- Inflammation
- Insulin and insulin sensitizers
- Repurposed drugs from other chronic conditions

Repurposed Drugs (20)

Herbal, Dietary Supplements, Nutraceuticals (11)

Behavioral Studies

ClinicalTrials.gov  August 2016
Aducanumab Therapy for Alzheimer’s Disease

Change in measurements of Amyloid B-protein over 54 weeks of trial demonstrating significant dose-response effect

Change in measurements of cognitive function (CDR-SB and MMSE) over 54 weeks of trial demonstrating significant treatment response

RVT-101 in Dementia with Lewy Bodies (DLB)

- 24-week Phase 2b study

Significant unmet need: no drugs approved in the U.S. or EU

Cholinergic deficits are a prominent feature of DLB

Increasing acetylcholine improves cognition and function in DLB

5HT$_{2A}$ activity is a driver of visual hallucinations

*Aricept was approved in Japan for the treatment of DLB in 2014*

*Cholinergic neurotransmission is more dysfunctional in DLB than Alzheimer’s disease*

*RVT-101 promotes the release of acetylcholine*

*RVT-101 inhibits the activity of the 5HT$_{2A}$ receptor*

Single successful study could serve as basis for approval of RVT-101 in DLB when combined with Alzheimer’s filing
Treatment Options

**Pharmacology**

- Cognitive Symptoms
  - Cholinesterase Inhibitors
  - Memantine (?)
- Motor Symptoms
  - Carbidopa/Levodopa
- Fluctuation and Attention
  - Modafinil, Armodafinil
- Behavior
  - Antidepressants
  - Atypical Antipsychotics
  - Prazosin (?)
  - Antiepileptics (?)
- Sleep
  - Melatonin
  - Clonazepam
- Autonomic
  - Fludrocortisone
  - Midodrine
  - Droxidopa

**Non-Pharmacology**

- Remove trigger, distract/redirect
- Caregiver education and support
- Adult day programs
- Psychotherapy techniques
  - Memory retraining
- Stimulation-oriented treatment
  - Music
  - Art
  - Recreational or social therapies
  - Exercise
  - Dance
  - Boxing
- Montessori-based activities
  - Memory BINGO
  - Group sorting

*Nearly all options are off-label use of medication*
Ongoing Prevention Trials

• Anti Amyloid Treatment in Asymptomatic Alzheimer’s (A4)
  • Individuals aged 65-86 with normal thinking and memory
  • Have positive AD biomarkers—amyloid deposition by PET scan
  • Three years of treatment with a monoclonal antibody against amyloid

• Alzheimer Prevention Initiative (API)
  • Individuals age 60-75 with normal thinking and memory
  • Have 2 copies of the ApoE e4 allele (high risk of AD)
  • Two years of treatment with a monoclonal antibody against amyloid

• TOMMORROW Study
  • Individuals age 65-83 with normal thinking and memory
  • Have polymorphism of TOMM40 gene (possibly increased risk of AD)
  • Five years of treatment with pioglitazone, an anti-diabetes drug

Source: www.ClinicalTrials.gov
In-Office Assessment

- Detailed History
  - From patient
  - From family
- Comprehensive Physical and Neurologic Examination
- Cognitive Evaluation
  - Global interview
  - Performance
- Lab work
- Imaging
• Memory impairment: repetitive; trouble remembering recent conversations, events, appointments; frequently misplaces objects

• Executive impairment: deterioration of complex task performance; decreased ability to solve problems; impaired driving

• Behavior, personality, mood changes

• Sleep changes

• Autonomic and constitutional changes

• Focal motor or sensory neurologic symptoms

• Drugs: alcohol, prescriptions, OTC medications

• Consideration of co-morbid disease
**Other Important Assessments**

**MOOD**

- Initially be evaluated with Patient Health Questionnaire (PHQ)-2
- Further investigation for a positive screen
- Can also use longer versions (PHQ-9)

<table>
<thead>
<tr>
<th>Over the past 2 weeks, how often have you been bothered by any of the following problems?</th>
<th>Not at all</th>
<th>Several Days</th>
<th>More Than Half the Days</th>
<th>Nearly Every Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**FUNCTION**

<table>
<thead>
<tr>
<th>In the Past 4 Weeks, Did the Subject Have Any Difficulty or Need Help With:</th>
<th>Not Applicable</th>
<th>Normal</th>
<th>Has Difficulty, But Does by Self</th>
<th>Requires Assistance</th>
<th>Requires Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Writing checks, paying bills or balancing a checkbook</td>
<td></td>
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<tr>
<td>2. Assembling a new record, business affairs, or other papers</td>
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<tr>
<td>3. Shopping alone for clothes, household necessities, or groceries</td>
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<tr>
<td>4. Playing a game of skill such as bridge or chess, working on a hobby</td>
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<tr>
<td>5. Heating water, making a cup of coffee, turning off the stove</td>
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<tr>
<td>6. Preparing a balanced meal</td>
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<tr>
<td>7. Keeping track of current events</td>
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<tr>
<td>8. Paying attention to and understanding a TV program, book, or magazine</td>
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<tr>
<td>9. Remembering appointments, family occasions, holidays, medications</td>
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<tr>
<td>10. Traveling out of the neighborhood, driving, or arranging to take public transportation</td>
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</tbody>
</table>

Kroenke K et al. (2003). *Medical Care*, 41(11),1284-1292
Laboratory Evaluation

- CBC, Full Chemistry, B\textsubscript{12}, TSH
- Current recommendation against RPR unless specific risk
- No value at the present time for genetic testing or ApoE genotyping
  - However may be valuable for therapy decisions and enrollment in clinical trials
- No CSF or serum biomarkers have established clinical validity
  - CSF biomarkers may assist in differential diagnosis
- Amyloid PET provides probability estimate that AD is present
  - May not change treatment decisions
  - Not covered by insurance at present time
- New AAN/APA Guidelines are currently in press
Neuroimaging changes correlate with cognitive decline.
Who Should Be Evaluated for AD and Why?

- People with risk factors
- People with memory or cognitive complaints, with or without a change in their everyday functioning
- Memory difficulties noted by close friend, spouse, or relative
- Depressed or anxious patients, with or without memory complaints
- Long term planning
- Medications may reduce symptom burden and slow progression
- Opportunity to participate in clinical trials
- Patient capable of contributing to medical, financial and social decision making process
## Stepwise Approach to Assessing AD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Purpose</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Pre-diagnostic Tests</td>
<td>Differential diagnosis and determination of co-existent disorders</td>
<td>Risk factor assessment, medical history, lab work, early warning signs</td>
</tr>
<tr>
<td>Step 2: Assess Performance</td>
<td>Cognitive assessments that help screen for and diagnose AD</td>
<td>Cognitive tests (MoCA, Mini-Cog) Informant tests (AD8, IQCODE)</td>
</tr>
<tr>
<td>Step 3: Assess daily function</td>
<td>Determine level of independence and degree of disability</td>
<td>Daily function assessment tools (IADL, FAQ)</td>
</tr>
<tr>
<td>Step 4: Assess behavioral symptoms</td>
<td>Determine presence and degree of behavioral symptoms</td>
<td>Behavioral assessment tools (NPI-Q)</td>
</tr>
<tr>
<td>Step 5: Identify caregiver and assess needs</td>
<td>Establish collaboration and assess adequacy of family and other support systems</td>
<td>Caregiver health, strength of relationship, burden, mood</td>
</tr>
<tr>
<td>Step 6: Special considerations</td>
<td>Identify culture, language, and health literacy of patient and caregiver</td>
<td>Differences in caregiver patterns, preferred language Health literacy : REALM</td>
</tr>
</tbody>
</table>

Algorithm for Long Term Follow-up

Screen
all elderly patients with memory complaint

Diagnose and treat
- Evaluate cognition, function and behavior
- Treat at time of diagnosis
- Consider implementing nonpharmacologic interventions

Perform
ongoing monitoring and evaluation

Re-evaluate
within 2 months and monitor every 6 months

Counsel
patients and caregivers about treatment expectations

Consider
potentially reversible causes of cognitive and/or functional impairment if a patient currently on antidementia therapy is showing signs of rapid decline

Provide
geriatric care management and counseling, and refer patients and caregivers to Alzheimer’s disease support groups

Mild
Consider treatment with a ChEI

Moderate
Consider treatment with a combination of ChEI + memantine

Severe
Consider treatment with memantine, add an approved ChEI as needed

Consider adding memantine to ChEI when patients progress from mild to moderate Alzheimer disease

Discontinue therapy when patients advance to loss of all cognitive and functional abilities
Playing board games such as chess, checkers, backgammon, or cards, is associated with a $1.6 \times$ risk reduction.
## Exercise and Dementia Risk

<table>
<thead>
<tr>
<th>Physical activity†</th>
<th>Cases/Controls</th>
<th>OR (95% CI)*</th>
<th>Cases/Controls</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>80/1103</td>
<td>1.00</td>
<td>110/1103</td>
<td>1.00</td>
</tr>
<tr>
<td>Low</td>
<td>21/485</td>
<td>0.67 (0.39-1.14)</td>
<td>28/485</td>
<td>0.64 (0.41-1.02)</td>
</tr>
<tr>
<td>Moderate</td>
<td>52/1360</td>
<td>0.67 (0.46-0.98)</td>
<td>79/1360</td>
<td>0.69 (0.50-0.95)</td>
</tr>
<tr>
<td>High</td>
<td>16/731</td>
<td>0.50 (0.28-0.90)</td>
<td>31/731</td>
<td>0.63 (0.40-0.98)</td>
</tr>
</tbody>
</table>

Test for trend: $P = 0.02$ for Alzheimer’s Disease and $P = 0.04$ for Any Dementia.

- High level of physical activity: 3 or more times per week at an intensity greater than walking
- Moderate level of physical activity: 3 or more times per week, but of an intensity equal to walking
- All other combinations considered low level of physical activity

Mediterranean diet (MeDi) adherence and the risk of Cognitive Impairment

Summary

• Early detection of disease affords opportunity for early intervention
• Combining interview- and performance-based assessments permit detection of early symptoms
• Physical exam, labs and imaging studies enhance confidence in diagnosis
• Current treatments provide symptomatic benefits
• Emerging therapies may help modify disease
• Do not forget use of non-pharmacologic approaches
• Use of algorithms assist in long-term planning and monitoring response to therapies and interventions