Myths and Realities of Dementia

What is dementia?

Alzheimer’s Dementia
  Prevalence
  Progression
  Neuropathology
Causes and Risk Factors
  Genes for Early and Late AD
    Amyloid Cascade Hypothesis
  Other Risks?
  Biomarkers
The Nun Study
Guam Disease
Repetitive Brain Trauma
Recommendations
Normal Cognitive Decline

Fig. 2.1 Life span performance on: (a) speed of processing measures; (b) working memory; (c) short-term memory; (d) long-term memory; (e) speed of processing; (f) mental knowledge.

Grammatical Complexity for Normal Group

Grammatical Complexity for Dementia Group
Dementias

Reversible:
- polypharmacy
- Carbon monoxide poisoning
- Infections: HIV, syphilis
- Metabolic disorders: hypoxia, thyroid disease, diabetes, dehydration & hyponatremia
- Nutritional: thiamine deficiency (Korsakoff's), anemia, folate, niacin
- Hematomas
- Hydrocephalus
- Depression

Progressive:
- Vascular: hypertension, ischemia
- Pick's/frontotemporal/repetitive brain trauma
- Parkinson's w/ and w/out Lewy body disease
- Huntington's
- ALS
- Guam disease
- 100s of rare dementias

Alzheimer's (50 – 70% of all dementias)

Parkinson's w/ & w/out Lewy Bodies (protein deposits)
- hunched posture, balance problems, rigid muscles
- confusions, hallucinations, delusions
- day-to-day and time of day variability

Frontotemporal Dementia/Pick's disease/Repetitive Trauma
- planning and judgment, emotional regulation & disinhibition
- language (primary progressive aphasia)
- shakiness, lack of coordination, spasms,
  gait and balance (progressive supranuclear palsy)

Vascular Dementia
- sudden onset, stepwise progression vs. gradual progression (small vessel disease)
Dr. Alois Alzheimer

1901: 51-year old
Memory problems, delusions, agitation, incontinence, speech & language problems
she died in 1906

Post-mortem: shrinkage of cortex, fatty deposits (plaques), dead brain cells

**figure 2:** Framingham Estimated Lifetime Risks for Alzheimer’s by Age and Sex

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>9.1%</td>
<td>12.2%</td>
</tr>
<tr>
<td>75</td>
<td>10.2%</td>
<td>18.5%</td>
</tr>
<tr>
<td>85</td>
<td>12.1%</td>
<td>20.3%</td>
</tr>
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</table>
Figure 13: Proportion of People Aged 65 and Older with Alzheimer's Disease and Other Dementias, by Race/Ethnicity, Washington Heights-Inwood Columbia Aging Project, 2006, N=2,162

Threshold Model: rate of decline, initial level imprecise criteria

Alzheimer's Disease

Cognitive function

Aging

Preclinical

MCI

Dementia

Years
Stage 1: no evident memory problems
Stage 2: occasional memory lapses, forgetting familiar words & names of everyday objects

**Stage 3: Mild Cognitive Impairment**

- amnestic-MCI /nonamnestic-MCI
- noticeable word-finding problems
- reading & comprehension problems
- problems with planning and organizing
- getting lost, losing objects
- problems with making change and simple tasks

**Stage 4: mild Alzheimer’s disease**

- impaired knowledge of recent events
- visual confusions, recognizing people
- impaired ability to perform mental calculations-counting backwards by 7s
- impaired performance on complex tasks
- shopping, paying bills, running errands
- personal history slips away
- socially withdrawn, emotional volatile
- poor judgment, bad decisions

**Stage 5: moderate Alzheimer’s disease**

- major gaps in memory
- confusions- day, date, place, people
- needs help: dressing, daily activities
- personality changes appear
**Stage 6: Severe Alzheimer’s disease**
unaware of surroundings or recent experiences
gaps, confusions, confabulations in personal
history
dressing, bathing, toileting, eating require help
sleep/wake disturbances
wandering, sun downing
personality changes: delusions, suspicions,
hallucinations, compulsions, questioning,
crying, aggression

**Stage 7: Late-stage Alzheimer’s disease**
incontinence
mute, unresponsive
walking, sitting, smiling, swallowing all affected

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**Neuropathology**

**Plaques**
The brain of the Alzheimer's patient will show
accumulations of a normal body-protein -
beta-amyloid - which has been transformed
into a form which is toxic to the brain. This
transformed beta-amyloid is found between
the nerve-cells of the brain and becomes
surrounded by the remnants of the cells which
it has killed forming so-called plaques.

**Tangles**
The other marker of Alzheimer's Disease is
known as a Neurofibrillary Tangle. This
tangle is caused by the build-up of a protein
called Tau inside the nerve-cells of the brain.
Brain shrinkage reveals the damage caused by Alzheimer's (right) compared to the normal brain (left).

**BRAIN ATROPHY VISUAL STANDARDS**

**GRADE = 1 (NONE, NL FOR AGE)**

**GRADE = 2 (MODERATE)**

**GRADE = 3 (SEVERE)**
Vertical sections through a normal (right) and a late stage Alzheimer’s brain (left) showing massive tissue loss and enlargement of cavities.

PET scans show differences in brain activity between a normal brain (left) and a brain affected by Alzheimer’s disease (right). Blue and black denote inactive areas.
Causes & Risk Factors

Figure 7.4 Survival time from mild cognitive impairment to dementia diagnosis by hippocampal volume at initial evaluation. $W =$ age-normalized volume.
Volga River Germans of Kansas
Figure 3. Pedigree of a family from Walter with Alzheimer's disease. Squares are males, circles are females. Black symbols had AD and cross-hatched symbols probably had AD. "A" indicates autopsy. Diagonal line through a symbol indicates death. Number below each symbol indicates age.
Early onset AD < age 50

Chromosome 14
Volga River Germans; people of Yarumal, Colombia
preselinin 1

Chromosome 1
preselinin 2

Chromosome 21
maybe linked to Down’s syndrome
Late Alzheimer's

Allen Roses

ApoE: protein for transport of cholesterol chromosome 19 implicated in both high blood pressure and families with ALZ

3 versions: E2, E3, E4
1 copy from each parent

<table>
<thead>
<tr>
<th>% w/ dementia</th>
<th>age at onset</th>
</tr>
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<tbody>
<tr>
<td>E2-E2</td>
<td>0%</td>
</tr>
<tr>
<td>E2-E3</td>
<td>19%</td>
</tr>
<tr>
<td>E3-E3</td>
<td>21%</td>
</tr>
<tr>
<td>E2-E4</td>
<td>20%</td>
</tr>
<tr>
<td>E3-E4</td>
<td>48%</td>
</tr>
<tr>
<td>E4-E4</td>
<td>81%</td>
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</table>

in “sporadics” with no known ALZ history: 64% have ApoE4

BUT: how many have ApoE4 and don't develop ALZ?

Swedish Nursing Homes: 0% of those with ALZ have ApoE4

Once Shunned, Test for Alzheimer's Risk Headed to Market

A Pennsylvania company is preparing to market a genetic test that will tell healthy people whether they are at risk of developing Alzheimer's disease. The test, called REVEL, is based on a genetic factor discovered by researchers at the University of Pennsylvania. The hereditary element, called ApoE, is a protein that transports cholesterol in the blood. REVEL is a test that identifies whether a person is carrying the ApoE gene, which is linked to an increased risk of developing Alzheimer's disease.

2/2 1%
2/3 3%
2/4 4%
3/4 20%
3/3 66%

It isn't helpful if there's nothing you can do about it.
TREM2 chromosome 6

.3 % of population, 2% of AD patients double mutation associated with ‘crumbling bones’ and sclerosing leukoencephalopathy (dementia marked by sexually inappropriate behavior)

Mutation causes white blood cells to no longer attack beta amyloid

ABCA7 chromosome 19

Mutation boosts production of cholesterol and lipids

Increases risk for AD more for Blacks than others

<table>
<thead>
<tr>
<th>Mutations and Susceptibility Genes Associated With Dementia, Their Locations, and Possible Pathways by Which Susceptibility Genes Might Influence Risk of Alzheimer’s Disease (AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Apolipoprotein E (APOE)</td>
</tr>
<tr>
<td>α2-macroglobulin (α2M)</td>
</tr>
<tr>
<td>Low-density lipoprotein receptor-related protein (LRP)</td>
</tr>
<tr>
<td>Insulin degrading enzyme (IDE)</td>
</tr>
<tr>
<td>Angiotensin I converting enzyme (ACE)</td>
</tr>
<tr>
<td>Interleukin 1 receptor alpha (IL-1α)</td>
</tr>
<tr>
<td>Adenosine triphosphate (ATP)-binding cassette transporter 1 (ABCA1)</td>
</tr>
<tr>
<td>Urolithin 1 (URO1)</td>
</tr>
<tr>
<td>Solute carrier-related receptor (S0011)</td>
</tr>
<tr>
<td>α-synuclein</td>
</tr>
<tr>
<td>Nocic3</td>
</tr>
<tr>
<td>Tau</td>
</tr>
</tbody>
</table>

CALHM1 (concentration of calcium in nerve cells, increases beta amyloid)
CLU, PICALM (CNS inflammation) CRI, BIN1 (protein transport), EPHA1, CD33, CD2AP, MS42A (linked to cholesterol, immune responses, endocytosis), CR1 (brain inflammation)
Increase risk

- Family history (esp. maternal)
- Being old (social isolation)
- Being female
- Exposure to pesticides and herbicides
- Drinking well water
  - mercury, aluminum, herbicides
- Farming, crop dusting, bauxite miners
- Diabetes

Not proven:
- aluminum from cans and cookware
- mercury in dental fillings

Protective factors

- education
- intelligence
- walking/exercise/cognitive activities
- CETP gene (larger cholesterol particles)

Not proven:
- red wine (resveratrol)
- low levels of homocysteine
- supplements: ginko
- omega 3 fatty acids
- antioxidants,
- NSAIDs
- B12 / Folic acid
- INSULIN /IGF- 1 gene

Increase risk ???

- Inhaled anesthetics
- Diabetes
- STATINS

Smoking: nicotinic acid
  (Parkinson’s)
- Tumeric (curcumin)
  (reduced risk in India,
  Singapore from curry?)
- Lack of CRFR1 gene (stress)
BIO-MARKERS: EARLY DIAGNOSIS

AMYLOID ACCRETION 5-10 years before diagnosis of Alzheimer’s dementia

Early on, a protein fragment called amyloid-beta aggregates on the brain causing loss of neuronal structures. The acrosomal deposit, amyloid plaques, destroy the synapses, leading to memory loss and cognitive decline. These plaques can be captured by cerebral imaging techniques like PET and MRI, allowing for early detection and intervention.

TAU BUILDUP 1-5 years before diagnosis

Before symptoms would appear, Alzheimer’s disease involves the misfolding and aggregation of brain cells, leading to cell death and loss of function. Early detection of tau protein accumulation, a hallmark of Alzheimer’s, can provide early intervention.

BRAIN SHRINKAGE 1-3 years before diagnosis

As the disease progresses, brain cells die, leading to atrophy and loss of cognitive function. This can be detected through imaging techniques like MRI, allowing for early intervention and management.

Appearance of Plaques vs. Dementia

Amyloid Plaques at Autopsy
Prevalence of AD Dementia

Percent positive (%) vs. Age (years)

Clinical Disease Stage
FDA-approved treatments

The first type, cholinesterase inhibitors, are designed to prevent the breakdown of acetylcholine, a chemical messenger important for memory and learning. They delay worsening of symptoms for six to 12 months for about half of the people who take them.

Three cholinesterase inhibitors are commonly used to treat mild to moderate Alzheimer's:

- Donepezil (Aricept®), approved in 1996
- Rivastigmine (Exelon®), approved in 2000
- Galantamine (Razadyne®), approved in 2001

The second type of drug works by regulating the activity of glutamate, a different messenger chemical involved in information processing:

- Memantine (Namenda®), approved in 2003
POSSIBLE COSTS OF EARLY DETECTION?

The Nun Study was a longitudinal study of aging and Alzheimer's disease funded by the National Institute on Aging. Participants were 678 American members of the School Sisters of Notre Dame religious congregation who were 75-103 years of age at the time the study began in 1990.
Aging with Grace:

The School Sisters of Notre Dame Study

by Sharon M. Reilly

I

In the early part of this century, 3,500 young women left their families in dozens and hundreds across the United States, vowing to remain celibate, renounce all earthly goods and deliberately follow their order, the School Sisters of Notre Dame. Most of these young Catholic nuns went on to earn college degrees and teach school, often becoming college presidents or seminary supervisors for the order. Nearly three-fifths of these women are still living today, ranging in age from 90 to 100. (In 1905, Sister Gertrude Saling, whose picture is on the second page, had just turned 21.

"Staying in touch with theirannuals about a group of nuns living to a ripe old age,"

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Sister Gertrude Saling as her first communion (above, left), at a ceremony for the School Sisters of Notre Dame (1910), left, with her four sisters (below, standing at the far left), who also became nuns (1903), and in 1975, eight years before her death.

OBSERVATION 2

33.1

FORECASTING ALZHEIMER’S DISEASE

Brain scans and writing samples may predict dementia

by KATHERINE PACEMAN

F

 freshmen, sophomore, junior or senior group leader who helped their group by giving them advice and guidance. (In 1905, Sister Gertrude Saling, whose picture is on the second page, had just turned 21."

A Way with Words

Auditing autobiographical sketches written by the sisters in their 20’s, before they took their vows, Smolander discovered that the number of ideas they packed into their sentences was a powerful predictor of who would develop Alzheimer’s 60 years later.

LOW IDEA DENSITY, HIGH RISK

I was in born in Eau Claire, Wis., on May 24, 1913, and was baptized in St. James Church. My father, Mr. E. A. Holczner, was born in the county of Racine, Ireland, and is now a street-car worker in Eau Claire.

HIGH IDEA DENSITY, LOW RISK

When I first told that I saw the light of day on a Tuesday night, there automatically ran through my mind the old nursery rhyme pretending to predict one’s fate by making it depend on the day of the week on which one was born.

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One way to ferret out a surging trend is to study the writing of young people. (In 1905, Sister Gertrude Saling, whose picture is on the second page, had just turned 21."

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Sister A

I was born in Eau Claire, Wis., on May 24, 1913 and was baptized in St. James Church. My father, Mr. L. H. Hallacher, was born in the city of Ross, County Cook, Ireland, and is now a sheet metal worker in Eau Clair. My mother, Katie Crosely, was born in Thorp, Wis. There are ten children in the family six boys and four girls. Two of the boys are dead.

I attended St. James grade and high school and made my First Holy Communion in June 1921 and was confirmed May 18, 1923 by Rt. Rev. Bishop Keane of De Pere, Wis. At the time of my entrance I was in good health and had had no serious illness before this time. The good example given to me by my teachers and the true religious spirit that they showed did much in directing my steps to Notre Dame.

I entered in August 1928 and was received June 17, 1932. I prefer teaching music to any other profession.

Sister B

The happiest day of my life so far was my First Communion Day which was in June nineteen hundred and twenty when I was but eight years of age and four years later in the same month I was confirmed by Bishop D. D. McGavick.

In nineteen hundred and twenty-six I was graduated from eighth grade and now my great desire of entering the convent was soon to be gratified. The following September at the age of fifteen, I came to Milwaukee to dear Notre Dame. The following vacation I spent with my parents. I visited the capitol in Madison and also the Motherhouse of the Franciscan Sisters of Perpetual Adoration at Duluth which visit increased my love for Notre Dame because it was and is Notre Dame.

At the close of my year of teaching at St. Pauls, I returned to the Motherhouse with all expectancy of being received. But I was offered to remain in the Candidature another year to finish my High School. It was considered a privilege but not until later did I fully realize and appreciate it. In nineteen hundred thirty-two I was admitted into the “hallowed precincts” of the Novitiate which was a happy, holy time. Now I am wandering about in “Dove’s Lane” waiting yet only three more weeks to follow in the footprints of my Spouse, bound to Him by the Holy Vows of Poverty, Chastity, and...
Impaired Performance on Cognitive Tests in Late Life by Linguistic Ability in Early Life

Late Life Survival by Linguistic Ability in Early Life
Guam Disease: Lytic-bodig disease
ALS plus Parkinson’s plus dementia

Chamorro people of Guam: paralysis, aphasia, irrational, manic/depression, catatonia

traditional food source: flour made from seeds of cycad

cycad seeds > fruit bats > bat soup

FRUIT BAT SOUP
Serves 4

- 3 fruit bats, well washed
- but neither skinned nor eviscerated
- Water
- 1 Tb finely sliced fresh ginger
- 1 large onion, quartered
- Sea salt to taste
- Chopped scallions
- Soy sauce and/or coconut cream

Dementia
Pugilistica
Repetitive Brain Trauma

A Late Hit for Pro Football Players

Emerging research suggests that hard hits on the field may cause delayed brain damage in retired athletes.

As a professional wrestler, Chris Nowinski had seen time in the business called "professional". Having repented, Chris observed a journey by Leong and Sas who sometimes entered the ring for a chance to thrill the audience, "I think I’d been around to watch them, but not often enough to know how much of an impact it might have on their bodies..."

Nowinski is an assistant professor of neurosurgery at Harvard Medical School, where he focused on concussions, back to the time when he was a student. He first became interested in the impact of repetitive brain trauma on athletes when he was working with former athletes and learning about the impact of repetitive brain trauma on the brain.

Nowinski is currently chief medical officer for the Family Reunification and Sports Safety organization, which provides brain injury assessments and support to athletes and their families.

Nowinski has a passion for the sport, and he also realizes the potential for brain injury in athletes. He has been working with retired athletes to help them understand the impact of repetitive brain trauma on their lives.

Nowinski is also working on a project to develop a new treatment for repetitive brain trauma, which he hopes will help athletes and their families.

Nowinski's research is supported by the National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health (NIH).

For more information, visit the website of the National Institute of Neurological Disorders and Stroke (NINDS).
REPETITIVE BRAIN TRAUMA
(chronic traumatic encephalopathy)

TAU Protein

Variant of fronto-temporal dementia
WHAT CAN I DO?

WHAT ABOUT...?
over-the-counter supplements
Herbals
‘nutraceuticals’ like ginko
resveratrol (red wine)
curcumin (turmeric)
“Nootropics” like piracetam
Caffeine & nicotine (gum or patches)
Multivitamins and mineral supplements
Folate
magnesium
omega 3 fatty acids
ADHD medications (Ritalin, Adderall)
May, 2010 NIA  
“consensus statement”

Preventing Alzheimer’s Disease and Cognitive Decline

No evidence for:
- Nutritional vitamins B, E, C; folate; beta-carotene
- Mediterranean diet
- Ginko biloba

Medication
- Statins
- Antihypertension drugs, anti-inflammatories

SES – childhood (education is inconsistent)

Engagement: social or cognitive

Past smoking

Limited evidence
- Reducing risk: omega-3 fatty acids

Increasing risk
- High blood pressure
- Diabetes
- Depression
- Loss of spouse
- Physical inactivity
- Current smoking
- Estrogen HRT

Available free at:

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Memory Fading?

Anacardium is wild cashew, a flowering shrub. What Homeopathy website says: The Anacardium patient is found mostly among the neurasthenics, such as have a type of nervous dyspepsia, relieved by food; depression, and irritability; diminution of sense of smell, sight, hearing. Syphilitic patients often present with these conditions. Intermittency of symptoms, fear of examination in students.

Baryta carb - well, here’s what Homeopathy says: Often useful in the dyspepsia of the young who have masturbated and who suffer from seminal emissions, together with cardiac irritability and palpitation. Affects glandular structures, and general degenerative changes, especially in arteries.

Kali phos is “salt” of potassium; generally used as fertilizers, detergents, pesticides
