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Epidemiology of Dementia

George W. Rebok, Ph.D.
December 8, 2010
Dementia (from the Latin *demens* meaning ‘without a mind’)

- Cognitive loss
- Functional loss
- Neuropsychiatric (behavioral) symptoms-NPS
Dementia has become a major public health concern

Leads to serious physical, functional, and psychologic morbidity, shortens life expectancy, and exacts a heavy burden on family caregivers

Has a broad economic impact; cost of dementia care estimated to be >100 billion dollars annually

Given projected increases in the prevalence of dementia over the next 50 years, it is critical to understand how it is assessed, diagnosed, and treated in the community
Dementia as a Public Health Issue

Dementia received little attention as a public health issue until several years ago.

Because it is primarily a disease of the elderly, impact on total life expectancy and health was considered minimal.

Because elderly who develop dementia are generally retired, impact on the economy was considered to be minimal.

Until recently, no knowledge base on strategies that might slow down the course of dementia.

Little realization of the economic costs of dementia.
Dementia

A. Diagnosis and Assessment
B. Symptomatic Course
C. Prevalence and Incidence
D. Risk and Protective Factors
Section A

Diagnosis and Assessment
Dementia: DSM-IV Diagnostic Criteria

Dementia is a syndrome

Essential feature of a dementia is the development of **multiple** cognitive deficits that include memory impairment (Amnesia) PLUS at least one of the following:

- **Aphasia**  
- **Apraxia**  
- **Agnosia**  
- **Disturbance in executive functioning**

The 4 “A”

Deficits must be sufficiently severe to cause impairment in occupational / social functioning (IADLs / ADLs) and must represent a decline from a previously higher level of functioning.
Functional loss

Ability to

• Use telephone
• Shop independently
• Manage own medications
• Handle finances
• Use transportation especially driving
• Conduct basic self care
Diagnosis of Dementia

Neuropsychiatric symptoms

- Sudden confusion
  - Delirium
- Mood disorders
  - Depression, anxiety, irritability, mania
- Psychotic disorders
  - Delusions, hallucinations
- Drive disturbances
  - Sleeping, feeding, sexuality
- Specific behaviors
  - Aggression, wandering, calling out
Diagnosis of dementia

- Largely clinically based
- **Diagnosis of dementia highly accurate**
- **Diagnosis of cause** less accurate
  - Probably AD 90-95% accurate
  - Possible AD 60-75% accurate
  - Much lower accuracy for other causes
  - >50% of cases are “mixed” in the real world
- **Alzheimer’s disease has pre-clinical phase**
  - No tests can detect this reliably yet
Multiple etiologies of dementia

- *Cortical versus subcortical dementia*

Dementia of the Alzheimer’s Type (AD) is a cortical dementia, and the most common form of dementia

Examples of subcortical dementia include Vascular dementia (formerly multi-infarct dementia) and dementia due to Parkinson’s disease
Cortical Dementia

- General cortical atrophy, especially in frontal & temporal lobes, with neuronal degeneration affecting particularly the three outer layers

Subcortical Dementia

- Lesions occur predominantly in the basal ganglia, brain stem nuclei & cerebellum
### Diagnosis of Dementia: Cortical versus subcortical dementia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cortical Dementia</th>
<th>Subcortical Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Speed of cognitive processing</td>
<td>Normal</td>
<td>Slowed (bradyphrenic)</td>
</tr>
<tr>
<td>• Attention</td>
<td>May be normal initially then deficits in selective, sustained &amp; divided attention</td>
<td>Usually globally impaired in early stages</td>
</tr>
<tr>
<td>• Frontal “executive abilities”</td>
<td>Usually preserved in early stages</td>
<td>Disproportionately impaired from onset</td>
</tr>
<tr>
<td>• Episodic memory</td>
<td>Severe amnesia</td>
<td>Forgetfulness</td>
</tr>
<tr>
<td></td>
<td>Recall &amp; recognition affected, normal forgetting</td>
<td>Recognition better than recall</td>
</tr>
<tr>
<td>• Language</td>
<td>Lexico-semantic deficits prominent</td>
<td>Normal except dysarthia and reduced output</td>
</tr>
<tr>
<td>• Visuo-spatial &amp; perceptual abilities</td>
<td>Impaired</td>
<td>Impaired (mild)</td>
</tr>
<tr>
<td>• Personality</td>
<td>Intact until late</td>
<td>Typically apathetic &amp; inert</td>
</tr>
<tr>
<td>• Mood</td>
<td>Usually normal*** / disinhibition present late</td>
<td>Depression common / disinhibition common early</td>
</tr>
</tbody>
</table>

From Craik & Tulving “The Handbook of Memory” (2005)
Diagnostic Features of AD

Cognitive deficits not due to other etiologies

★ Central nervous system (cerebrovascular, Parkinson’s, Huntington’s diseases)
★ Systemic (hypothyroidism, vitamin deficiency, HIV)
★ Acute events (head trauma)

Definitive diagnosis made at autopsy with the finding of beta amyloid plaques and neurofibrillary tau tangles
Beta-amyloid plaques

- Protein fragments snipped from a larger protein called amyloid precursor protein (APP)
- Found in the hippocampus & other cortical areas in AD patients
- Don’t know if plaques cause AD or are a by-product of the AD process

Neurofibrillar Tangles

- In healthy neurons, tau makes microtubules stable
- In AD, tau is chemically altered and tangles with other tau threads
- Causes a collapse in neuron transport system, first resulting in poor communication between neurons, and later cell death
Section B

Symptomatic Course
Symptomatic Course of AD

AD is characterized by a gradual onset with a continual cognitive decline.

Personality changes may include:
- *Increased irritability*
- *Depression, perhaps as a prodromal feature*

Generalized cortical atrophy on CT/MRI.
Alzheimer Deterioration

ALZHEIMER DETERIORATION ON THE MINI-MENTAL STATE EXAM OVER TIME

SCORE

30
20
10
0

AVERAGE TIME OF ILLNESS (years)

-5
0
5
10
Changes in Brain Metabolism with AD

PET Scan of Normal Brain

PET Scan of AD Brain

MCI first operationally defined by Flicker et al. (1991), later redefined by Petersen et al. 1999

Is Mild Cognitive Impairment (MCI) early / prodromal AD or distinct diagnostic entity?

- Morris JC et al. argues MCI represents early-stage AD
- Petersen RC et al. argues MCI is distinct entity, can transition back to normal or AD

MCI – Amnestic Type (MCIa) is most common form

- Characterized by isolated memory impairment and subjective memory complaint, but no ADL impairment (IADLs not well operationalized)
## Prevalence of MCI

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>age</th>
<th>Diagnostic Criteria</th>
<th>Prevalence Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frisoni 2000</td>
<td>1,435</td>
<td>75-95</td>
<td>MCI</td>
<td>15</td>
</tr>
<tr>
<td>Ritchie 2001</td>
<td>833</td>
<td>≥60</td>
<td>MCI</td>
<td>3</td>
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<tr>
<td>Hanninen 2002</td>
<td>1,150</td>
<td>60-76</td>
<td>MCI</td>
<td>5.3</td>
</tr>
<tr>
<td>Busse 2003</td>
<td>1,045</td>
<td>≥75</td>
<td>MCI</td>
<td>3.1</td>
</tr>
<tr>
<td>Busse 2003</td>
<td>1,045</td>
<td>≥75</td>
<td>MCI w/o SMC</td>
<td>5.1</td>
</tr>
<tr>
<td>Fisk 2003</td>
<td>1,790</td>
<td>≥65</td>
<td>MCI</td>
<td>1.03</td>
</tr>
<tr>
<td>Fisk 2003</td>
<td>1,790</td>
<td>≥65</td>
<td>MCI w/o SMC</td>
<td>3.02</td>
</tr>
<tr>
<td>Lopez 2003</td>
<td>3,608</td>
<td>≥65</td>
<td>MCI</td>
<td>19</td>
</tr>
<tr>
<td>Lopez 2003</td>
<td>927</td>
<td>≥65</td>
<td>MCIa</td>
<td>6</td>
</tr>
<tr>
<td>Ganguli 2004</td>
<td>1,248</td>
<td>≥65</td>
<td>MCI</td>
<td>3.2</td>
</tr>
<tr>
<td>Solfrizzi 2004</td>
<td>2,963</td>
<td>65-84</td>
<td>MCI</td>
<td>3.2</td>
</tr>
</tbody>
</table>
## Conversion from MCI to AD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Source</th>
<th>Mean Age</th>
<th>N</th>
<th>Conversion To:</th>
<th>Mean follow-up (months)</th>
<th>Annual Conversion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tierney 1996</td>
<td>Clinic</td>
<td>73.9</td>
<td>138</td>
<td>NINCDS-ADRDA AD AD</td>
<td>24</td>
<td>10.9</td>
</tr>
<tr>
<td>Huang 2000</td>
<td>Clinic</td>
<td>61.2</td>
<td>31</td>
<td>NINCDS-ADRDA AD AD</td>
<td>26</td>
<td>22.5</td>
</tr>
<tr>
<td>Li 2001</td>
<td>Community</td>
<td>68.7</td>
<td>19</td>
<td>Clinical Dx of AD AD</td>
<td>44</td>
<td>13.5</td>
</tr>
<tr>
<td>Morris 2001</td>
<td>Community</td>
<td>76.4</td>
<td>53</td>
<td>CDR &gt;= 1 AD AD</td>
<td>61</td>
<td>4.0</td>
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<tr>
<td>Ritchie 2001</td>
<td>Community</td>
<td>&gt;65</td>
<td>308</td>
<td>DSM-III R AD AD</td>
<td>24</td>
<td>5.6</td>
</tr>
<tr>
<td>Amieva 2004</td>
<td>Community</td>
<td>50-85</td>
<td>90</td>
<td>DSM-III R AD AD</td>
<td>24</td>
<td>16.1</td>
</tr>
<tr>
<td>Tabert 2006</td>
<td>Clinic</td>
<td>&gt;65</td>
<td>148</td>
<td>NINCDS-ADRDA AD AD</td>
<td>36</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(16.6 MCIa)</td>
</tr>
</tbody>
</table>
Symptomatic Course of AD

**AAMI:** Age-associated memory impairment
- Memory 1 SD below young norms

**MCIa:** (Amnestic) mild cognitive impairment
- Memory 1.5 SD below peer norms

**AACD:** Age-associated cognitive decline
- 1 cognitive domain 1 SD below peer norms

**CIND:** Cognitive impairment not dementia
- ≥1 cognitive domain(s) impaired

Adapted by CTLT from Feldman & Jacova, 2005.
Section C

Prevalence and Incidence of AD
In 2001, an estimated 24 million people with dementia in the world (Ferri, Prince, Brayne et al., 2005)

Majority of people with dementia are living in the developing world

Proportion of people with dementia in developing nations will rise from 61% in 2000 to 65% in 2020 and 71% in 2040.

China and its Pacific neighbors have highest number of people with dementia (6 million) followed by European Union (5 million), USA (2.9 million), and India (1.5 million)
Global dementia prevalence in people aged 60+ estimated at 3.9% (Ferri, Prince, Brayne et al. 2005)

Prevalence varies by region: Africa (1.6%), Eastern Europe (3.9%), China (4.0%), Latin America (4.6%), Western Europe (5.4%), North America (6.4%)

Similar pattern of dementia subtypes across the world, with AD accounting for 50-70% and VaD accounting for 15-25%.

Global dementia incidence estimated to be about 7.5 per 1000 population

Incidence rates of dementia across regions are similar in younger-old (< 75 years), but vary more among the older-old
As with all psychiatric disorders, must keep in mind:

- **Setting** *(clinic, community, population-based)*
- **Diagnostic criteria** *(DSM-IV, ICD-10, NINCDS-ADRDA, NINDS-AIREN)*
- **Length of follow-up for incidence studies*
### Prevalence of AD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>N</th>
<th>Diagnosis</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSHA 1994</strong></td>
<td>65+</td>
<td>10,263</td>
<td>NINCDS- ADRDA</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td></td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>85+</td>
<td></td>
<td></td>
<td>34.5</td>
</tr>
<tr>
<td><strong>Ebly 1994 - CSHA</strong></td>
<td>85+</td>
<td>1,835</td>
<td>NINCDS- ADRDA</td>
<td>28.5</td>
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<tr>
<td></td>
<td>85-89</td>
<td>1,332</td>
<td></td>
<td>23</td>
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<tr>
<td></td>
<td>90-95</td>
<td>371</td>
<td></td>
<td>40</td>
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<tr>
<td></td>
<td>95+</td>
<td>104</td>
<td></td>
<td>58</td>
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<tr>
<td><strong>Breitner 1999 – Cache County</strong></td>
<td>65+</td>
<td>5,092</td>
<td>NINCDS- ADRDA</td>
<td>6.45</td>
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<tr>
<td></td>
<td>65-69</td>
<td>~1200</td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>70-74</td>
<td>~1200</td>
<td></td>
<td>2.28</td>
</tr>
<tr>
<td></td>
<td>75-79</td>
<td>~1000</td>
<td></td>
<td>4.47</td>
</tr>
<tr>
<td></td>
<td>80-84</td>
<td>~800</td>
<td></td>
<td>10.43</td>
</tr>
<tr>
<td></td>
<td>85-89</td>
<td>~500</td>
<td></td>
<td>18.95</td>
</tr>
<tr>
<td></td>
<td>90+</td>
<td>~300</td>
<td></td>
<td>27.76</td>
</tr>
</tbody>
</table>
Prevalence of AD

Prevalence appears to double approximately every 5.1 years (Jorm et al. 1987)

In older age groups, there may be a gender difference in prevalence

- *Is this a real difference, or due to women living longer than men?*
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>N</th>
<th>Diagnosis</th>
<th>Incidence *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawas 2000 – BLSA</td>
<td>55+</td>
<td>1,236</td>
<td>NINCDS-ADRDA</td>
<td>1.23% / yr</td>
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<tr>
<td></td>
<td>60-64</td>
<td></td>
<td></td>
<td>0.08% / yr</td>
</tr>
<tr>
<td></td>
<td>65-69</td>
<td></td>
<td></td>
<td>0.13% / yr</td>
</tr>
<tr>
<td></td>
<td>70-74</td>
<td></td>
<td></td>
<td>0.42% / yr</td>
</tr>
<tr>
<td></td>
<td>75-79</td>
<td></td>
<td></td>
<td>0.89% / yr</td>
</tr>
<tr>
<td></td>
<td>80-84</td>
<td></td>
<td></td>
<td>2.16% / yr</td>
</tr>
<tr>
<td></td>
<td>85+</td>
<td></td>
<td></td>
<td>6.48% / yr</td>
</tr>
<tr>
<td>Miech 2002 – Cache County</td>
<td>65+</td>
<td>3,308</td>
<td>NINCDS-ADRDA</td>
<td>16.81</td>
</tr>
<tr>
<td></td>
<td>69-71</td>
<td></td>
<td></td>
<td>1.97</td>
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<td></td>
<td>72-74</td>
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<td>6.03</td>
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<td>75-77</td>
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<td>9.24</td>
</tr>
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<td></td>
<td>78-80</td>
<td></td>
<td></td>
<td>18.84</td>
</tr>
<tr>
<td></td>
<td>81-83</td>
<td></td>
<td></td>
<td>36.01</td>
</tr>
<tr>
<td></td>
<td>84-86</td>
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<td>57.91</td>
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<td>87-89</td>
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<td>73.28</td>
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<td>96.11</td>
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<tr>
<td></td>
<td>93+</td>
<td></td>
<td></td>
<td>73.58</td>
</tr>
<tr>
<td>Ravaglia 2005 – CSBA</td>
<td>65+</td>
<td>937</td>
<td>NINCDS-ADRDA</td>
<td>23.8</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
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<td></td>
<td>11.3</td>
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<td>75-84</td>
<td></td>
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<td>28.1</td>
</tr>
<tr>
<td></td>
<td>85-94</td>
<td></td>
<td></td>
<td>75.8</td>
</tr>
</tbody>
</table>

* Incidence per 1,000 person-years unless noted
Anchor point—annual incidence is ~1% between ages 75–79

Incidence appears to double approximately every 5 years (Jorm et al. 1998)

Incidence increases with age, but then may peak and then decline among extremely old (Miech et al. 2002)

- Decline may begin in early 90s for men, mid-to-late 90s for women
- Is this real, due to healthy lifestyle, other?  [AMIR FAYEK]
Why Is There a Late Decline in Incidence?

Declines may reflect results from a “mixed” population that includes individuals who are relatively invulnerable to AD

There may be selective censorship of individuals with risk factors for AD, e.g., ASCVD
Looming Growth in the Prevalence of AD

World populations are aging rapidly

Prevalence is a function of both incidence and duration

Duration of prevalent cases is being extended

Unintended consequences of new drugs that stabilize and prolong life after onset of AD
Growth of Persons Age 65+ in the U.S.

Population of Persons Age 65 and Over: 1990 to 2050
Middle Series Beyond 1990

Future Estimates of Prevalence of AD in the U.S.

Based on the 2000 U.S. Census, low, middle, and high estimates for 65+

<table>
<thead>
<tr>
<th>Year</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>5.1</td>
<td>5.1</td>
<td>5.3</td>
</tr>
<tr>
<td>2020</td>
<td>5.5</td>
<td>5.7</td>
<td>6.2</td>
</tr>
<tr>
<td>2030</td>
<td>7.2</td>
<td>7.7</td>
<td>8.6</td>
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<tr>
<td>2040</td>
<td>10.0</td>
<td>11.0</td>
<td>12.8</td>
</tr>
<tr>
<td>2050</td>
<td>11.3</td>
<td>13.2</td>
<td>16.0</td>
</tr>
</tbody>
</table>

Hebert LE et al., 2003
### Potential Effects of Intervention to Delay Onset Prevalent Cases (U.S.)

<table>
<thead>
<tr>
<th>Risk Ratio</th>
<th>Mean Delay</th>
<th>2007</th>
<th>2027</th>
<th>2047</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>0</td>
<td>2.89</td>
<td>4.74</td>
<td>8.64</td>
</tr>
<tr>
<td>0.90</td>
<td>1.0</td>
<td>2.68</td>
<td>4.31</td>
<td>8.26</td>
</tr>
<tr>
<td>0.75</td>
<td>2.0</td>
<td>2.32</td>
<td>3.64</td>
<td>6.70</td>
</tr>
<tr>
<td>0.50</td>
<td>5.0</td>
<td>1.74</td>
<td>2.49</td>
<td>4.60</td>
</tr>
</tbody>
</table>

Brookmeyer et al., 1998

[LINGSHENG LI]
Total costs associated with AD estimated about $47,000/yr in 1990 dollars (includes direct costs of nursing care and paid home care as well as unpaid home care)

An average one-year delay in disease onset would result in annual savings of about $10 billion at 10 years after initiation of intervention
Even a six-month delay would correspond to an annual savings of about 4.7 billion at 10 years and nearly $18 billion annually after 50 years

Estimates may be biased

Brookmeyer et al., 1998
Section D

Risk & Protective Factors of AD
**Risk Factors for AD**

**Age**

[ALEXANDRA KUEIDER]

- Older age increases risk for AD, and may affect rate of progression

**Gender**

- In some studies, women have an increased incidence of AD compare to men, suggesting that gender may be a risk factor
- Other support comes from reports on estrogen replacement protecting against AD
- However, most studies, when controlling for longevity differences, have not found gender to be a significant risk factor (e.g., Kawas et al. 2000; Edland et al. 2002)
Age- and Sex-Specific Incidence Rates of Alzheimer Disease and Dementia in Rochester, MN, During 1985 through 1989

Age- and Sex-Specific Incidence Rates of Alzheimer Disease

- Solid lines: Males
- Dotted lines: Females

- Stockholm, Sweden
- Southwestern France
- Europe, pooled data
- Baltimore, MD
- Framingham, MA
- Rochester, MN

## Cardiovascular risk factors and AD

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Factor</th>
<th>N</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kivipelto et al., 2001</td>
<td>Midlife hypertension</td>
<td>1400</td>
<td>aOR 2.8 (1.1 – 7.2)</td>
</tr>
<tr>
<td>Ruitenbergen et al. 2001</td>
<td>History of hypertension</td>
<td>5,468</td>
<td>aRR 1.4 (1.1 – 1.8)</td>
</tr>
<tr>
<td>Kivipelto et al., 2001</td>
<td>Midlife high total cholesterol</td>
<td>1400</td>
<td>aOR 2.2 (1.0 – 4.7)</td>
</tr>
<tr>
<td>Reitz et al., 2005</td>
<td>Late life high total cholesterol</td>
<td>1168</td>
<td>aOR 1.55 (0.75 – 3.19)</td>
</tr>
</tbody>
</table>
Cardiovascular risk factors and AD

Hypertension

- **Midlife hypertension is positively related to AD**
- **History of hypertension, when assessed at baseline in incidence studies, has a weak, but consistently positive association**

Lipid levels

- **Midlife levels of total cholesterol associated with increase prevalence of AD in late-life**
- **High levels in late life are less consistent**
Diabetes Mellitus (DM)

- DM is associated with cognitive decline, and with increased risk of stroke & vascular dementia
- Relationship between DM & AD less clear, some studies show relationship, others do not
- May be due to differences in age, ethnicity, sex, study design, length of follow-up, criteria used to define DM and AD, etc
Obesity

- Associated with vascular disease, but role as risk factor for AD is conflicting
- No association between midlife obesity and late-life AD found in 3 longitudinal epidemiologic studies with 20+ years follow-up (HAAS, CRFADS, JAHS)
- Swedish Longitudinal Population Study found significant association between overweight at age 70 and incident AD in following 10-18 years in women only
Stroke

- Cardiovascular Health Study reported that presence of angina, myocardial infarction, and peripheral arterial disease associated with higher risk of AD
- Association between stroke and AD may be even stronger for those with hypertension and / or diabetes (Honig et al., 2003)
Genetic – early onset (familial, autosomal dominant)

- Associated with mutations in APP, PSEN1, PSEN2

Genetic – late onset AD

- Associated with one allelic form of apolipoprotein E gene (APOE) – the \( \varepsilon4 \) allele
- However, \( \varepsilon4 \) only modifies risk, is not sufficient cause
APOE

- APOE is localized on chromosome 19
- Three alleles *E2, *E3, *E4
- Globally, APOE shows substantial allelic variation with ranges from 0-20% for *E2, 60-90% for *E3, and 10-20% for *E4 (Singh et al., 2006)
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Typical Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε4/ε4</td>
<td>~ 2% are ε4/ε4</td>
</tr>
<tr>
<td>ε4/ε3</td>
<td>~ 24% are ε4/ε3</td>
</tr>
<tr>
<td>ε4/ε2</td>
<td>~2% are ε4/ε2</td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>~ 61% are ε3/ε3</td>
</tr>
<tr>
<td>ε3/ε2</td>
<td>~ 11% are ε3/ε2</td>
</tr>
<tr>
<td>ε2/ε2 (very rare)</td>
<td></td>
</tr>
</tbody>
</table>
Those with ε4/ε4 tend to get AD between 65–80 and have 15-fold risk, (vs. ε3/ε3) after adjustment for age.

Those with ε4/ε3 tend to get AD between 75 and 90 and have 3-4 fold risk.

The ε2 allele may confer decreased risk.
Diet

- Lower caloric intake may reduce risk of AD, especially for those with the ε4 allele (Luchsinger JA et al., 2002)
- Dietary patterns may confer reduced risk for AD, particularly the Mediterranean diet (Scarmeas et al., 2006)
- Weekly fish consumption may reduce risk of AD by 60% compared with those who rarely eat fish (Morris MC et al., 2003)
  - However, greater benefit may be for those without the ε4 allele (Huang et al., 2005)
Exercise / Physical Activity

- Prospective studies have found an association between higher levels of physical activity and AD (e.g., Laurin et al., 2001)
- Incident rate of dementia lower for those who exercise 3+/week compared to those who exercise less than 3x/week (HR 0.62, 95% CI 0.44 – 0.86) (Larson et al., 2006)
- Problems incl. that exercise is normally self-report and usually in late-life
Education

- Several epidemiologic studies suggest that higher level of education is protective against AD
- Relative risk for low versus high education and AD is 1.80 (95% CI 1.43, 2.27)
- Relative risk for low and medium education versus high and AD is 1.44 (95% CI 1.24 – 1.67)

Caamaño-Isorna et al., 2006
Occupational attainment

- **Low lifetime occupational attainment may increase risk of AD** (RR 2.25, 95% CI 1.32 – 3.06) (Stern et al., 1994)

- **Risk may be greatest for those with both low educational and occupational attainment**
Social engagement / leisure activities

- Late-life participation in cognitively stimulating activities associated with 64% reduction in risk of incident AD (OR 0.36, 95% CI 0.20 – 0.65) (Wilson RS et al., 2002)
- Data from the Kungsholmen project suggests that late-life participation in any stimulating activity, either mentally or socially oriented, may be associated 50% reduction in risk of dementia (Wang et al., 2002)
Social engagement / leisure activities, cont.

- However, must consider whether no engagement in late-life is associated with prodromal AD

- No association found between midlife social engagement and incident dementia in Honolulu-Asia Aging Study (Saczynski et al., 2006)
Cognitive reserve (CR)

• *Brain actively attempts to cope with brain damage (i.e., AD pathology) by using preexisting cognitive processing approaches or by enlisting compensatory approaches*

• *Individuals with more CR would be more successful at coping with the same amount of brain damage*

• *CR may modulate clinical expression of AD pathology*
Cognitive Reserve, continued

- **Neural implementation of CR might take one of 2 forms:**
  - **Neural reserve** – *brain networks or cognitive paradigms that are less susceptible to disruption, because more efficient or have greater capacity*
    - Helps cope with brain pathology
  - **Neural compensation** – *the process by which individuals suffering from brain pathology use brain structures / networks (and thus cognitive strategies) not normally used by healthy individuals*

*Stern et al., 2005*
Cognitive Reserve, continued

- **Educational attainment, socioeconomic status (including occupational attainment, income), and IQ are commonly used proxies for CR**

- **Can directly enhancing CR prevent or delay the diagnosis of AD?**

  [BRANDON JOHNSON]
Major Challenges for the Future

- Strengthening interdisciplinarity
- From epidemiology among the elderly to epidemiology in aging research
- Large-scale longitudinal studies of cognitively normal individuals over time
- Epidemiology of medical and nursing care
- Translating epidemiologic study of dementia into the practice of prevention