Alzheimer’s Disease & Long Term Care:
a case study

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University College Dublin
Aims of the Study

1. Update previous work, using actual data on individual Alzheimer’s Disease (AD) patients
2. Estimate financial impact of medical interventions
3. Review genetic links other than APOE
Thanks

- Prof. Angus Macdonald
- Dr. Delme Pritchard
- The Actuarial Profession
- Prof. David Wilkie
1907, after Dr. Alois Alzheimer, who noticed abnormalities in the brain of a mental patient.

Irreversible, progressive brain disease that slowly destroys memory and thinking skills.

Although the risk of developing AD increases with age, AD is not a part of normal aging.
More on AD

- **Mild AD**
  - memory loss
  - confusion
  - trouble handling money
  - poor judgment
  - mood changes
  - increased anxiety

- **Moderate AD**
  - increased memory loss and confusion
  - problems recognizing people
  - difficulty with language and thoughts
  - restlessness
  - agitation
  - wandering
  - repetitive statements
More on AD

- **Severe AD**
  - extreme brain shrinkage
  - patients are completely dependent on others
  - weight loss
  - seizures
  - skin infections
  - groaning, moaning, or grunting

- increased sleeping
- loss of bladder and bowel control

- **Death usually occurs from aspiration pneumonia or other infections**
Some numbers

- Ireland: 35,000 AD patients
- UK: >500,000 patients
  Annual cost ≈ £5 billion
- USA: 4.5 million patients
  Annual cost : $100 billion

- For every 5-year age group beyond 65, the percentage of people with AD doubles.
- By 2050, 13.5 million older Americans are expected to have AD
Causes & cures

- Cause unknown

- 2 abnormal brain structures
  - beta-amyloid plaques
  - neurofibrillary tangles
Causes & cures

- No cure
  - Treatments largely symptomatic
- Irreversible??
  - One recorded recovery!
“We apologise to the swindler and con-artist Ernest Saunders for suggesting that he pretended to have Alzheimer’s Disease in order to procure an early release from prison”
Markov model for AD

**State 1:**
No Alzheimer’s disease

**State 2:**
Onset of AD

**State 3:**
Institutionalised from AD

**State 4:**
Dead

\[ \mu_{12} \]
\[ \mu_{23} \]
\[ \mu_{34} \]
\[ \mu_{41} \]

Markov model for AD

$\mu_x^{14} = 65\% \text{ AM80}, 65\% \text{ AF80}$

$\mu_x^{24} = 0.335^* \mu_x^{14}$

$\mu_x^{34} = 0.17^+ \mu_x^{14}$

$\mu_x^{12} = \exp(1.31E-07+0.146x)$

$\mu_x^{23} = 0.189$
New data

Affiliated to Duke University


70+ academic publications using the data

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>448</td>
<td>160</td>
</tr>
<tr>
<td>Female</td>
<td>646</td>
<td>303</td>
</tr>
<tr>
<td>Total</td>
<td>1,094</td>
<td>463</td>
</tr>
<tr>
<td></td>
<td>E2</td>
<td>E3</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Male</td>
<td>1,058</td>
<td>455</td>
</tr>
<tr>
<td>Female</td>
<td>1,440</td>
<td>693</td>
</tr>
<tr>
<td>Total</td>
<td>2,498</td>
<td>1,148</td>
</tr>
</tbody>
</table>
Rate of institutionalisation

<table>
<thead>
<tr>
<th>Test</th>
<th>$\chi^2$</th>
<th>M-W</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.25</td>
<td>0.06</td>
<td>0.49</td>
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</tbody>
</table>
Rate of institutionalisation

![Graph showing the rate of institutionalisation with age]

Mu23_hat

Combined

Age

Mu23
Rate of death pre-institutionalisation

<table>
<thead>
<tr>
<th>Test</th>
<th>$\chi^2$</th>
<th>M-W</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.16</td>
<td>&lt;0.01</td>
<td>0.03</td>
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</table>
Rate of death post-institutionalisation

<table>
<thead>
<tr>
<th>Test</th>
<th>$\chi^2$</th>
<th>M-W</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.016</td>
</tr>
</tbody>
</table>
Fitting Models

- Gompertz-Makeham family
  - Mortality
  - Critical illness

\[ \mu^i_j = \text{Polynomial1} + \exp(\text{Polynomial2}) \]

\[ \mu^i_j = \alpha_1 + \alpha_2 x + \ldots + \alpha_r x^{r-1} + \exp(\beta_1 + \beta_2 x + \ldots + \beta_s x^{s-1}) \]
Fitting Models

Obtain maximum likelihood estimates for the GM parameters

\[ L(\mu_x^{ij}) = \prod_x e^{-\mu_x E_x^{ci} (\mu_x^{ij})^\theta_x^{ij}} \]

\[ \log_e L(\mu_x^{ij}) = \sum_x \theta_x^{ij} \log_e \mu_x^{ij} - E_x^{ci} \mu_x^{ij} \]

Use likelihood ratio test to determine number of parameters needed
### Detailed Example

#### \( \mu^{34} \) Female

<table>
<thead>
<tr>
<th></th>
<th>Model</th>
<th>(-2 \log L)</th>
<th>Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GM(1,0)</td>
<td>646.7</td>
<td>1 vs. 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>GM(2,0)</td>
<td>635.7</td>
<td>2 vs. 3</td>
<td>0.003</td>
</tr>
<tr>
<td>3</td>
<td>GM(3,0)</td>
<td>626.8</td>
<td>3 vs. 4</td>
<td>0.918</td>
</tr>
<tr>
<td>4</td>
<td>GM(4,0)</td>
<td>626.8</td>
<td>2 vs. 5</td>
<td>0.012</td>
</tr>
<tr>
<td>5</td>
<td>GM(2,2)</td>
<td>626.9</td>
<td>5 vs. 6</td>
<td>0.08</td>
</tr>
<tr>
<td>6</td>
<td>GM(0,2)</td>
<td>631.9</td>
<td>6 vs. 7</td>
<td>0.039</td>
</tr>
<tr>
<td>7</td>
<td>GM(1,2)</td>
<td>627.7</td>
<td>7 vs. 5</td>
<td>0.375</td>
</tr>
<tr>
<td>8</td>
<td>GM(1,3)</td>
<td>626.9</td>
<td>7 vs. 8</td>
<td>0.38</td>
</tr>
<tr>
<td>9</td>
<td>GM(0,3)</td>
<td>627.0</td>
<td>6 vs. 9</td>
<td>0.027</td>
</tr>
<tr>
<td>10</td>
<td>GM(0,4)</td>
<td>627.0</td>
<td>9 vs. 10</td>
<td>0.976</td>
</tr>
</tbody>
</table>
Detailed Example cont.

\[
\mu_x^{34} = 0.105 + \exp(-16.220 + 0.166x)
\]
Detailed example cont.

Mu34 female GM(1,2) standardised residuals

age

residuals
## Diagnostic tests

<table>
<thead>
<tr>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\chi^2$</td>
<td>0.53</td>
</tr>
<tr>
<td>Std. residuals</td>
<td>0.39</td>
</tr>
<tr>
<td>Signs</td>
<td>0.41</td>
</tr>
<tr>
<td>Change of signs</td>
<td>0.37</td>
</tr>
<tr>
<td>Grouping of signs</td>
<td>0.45</td>
</tr>
<tr>
<td>Serial correlations</td>
<td>0.43</td>
</tr>
</tbody>
</table>
Other transition intensities

\[ \mu_{x}^{23} = \exp(-2.92 + 0.016x) \]
Other transition intensities

Mu23 agg GM(0,2) std residuals

-4 -2 0 2 4

age

residuals
Other transition intensities

\[ \mu_x^{24} = \exp(-8.17 + 0.071x) \]
Other transition intensities

Mu24 male GM(0,2) standardised residuals

age

residuals
Other transition intensities

\[ \mu_x^{24} = 0.029 + \exp(-22.01 + 0.221x) \]
Other transition intensities

Mu 24 female GM(1,2) standardised residuals

Residual

Age
Other transition intensities

\[
\mu_x^{34} = \exp(-5.14 + 0.052 x)
\]
## Summary of Fitted Models

<table>
<thead>
<tr>
<th>Transition</th>
<th>Sex</th>
<th>Model</th>
<th>p-value ($\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu^{23}$</td>
<td>aggregate</td>
<td>GM(0,2)</td>
<td>0.73</td>
</tr>
<tr>
<td>$\mu^{24}$</td>
<td>male</td>
<td>GM(0,2)</td>
<td>0.96</td>
</tr>
<tr>
<td>$\mu^{24}$</td>
<td>female</td>
<td>GM(1,2)</td>
<td>0.61</td>
</tr>
<tr>
<td>$\mu^{34}$</td>
<td>male</td>
<td>GM(0,2)</td>
<td>0.30</td>
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<tr>
<td>$\mu^{34}$</td>
<td>female</td>
<td>GM(1,2)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Based on grouped data with (expected > 5)
Summary female mortality

mu-x female

0
0.1
0.2
0.3
0.4 0.5
60 65 70 75 80 85 90

Age

mu-x

mu_14
mu_24
mu_34

mu-x4 female

Age
CERAD vs M & P

mu-23 aggregate

mu_x

Age

0
0.05
0.1
0.15
0.2
0.25

60 70 80 90

CERAD GM02
McD&P GM10
CERAD GM10
CERAD vs M & P

mu-24

Age

mu_x

CERAD male
CERAD female
McD&P male
McD&P female
CERAD vs M & P

mu-34

mu_x

60 70 80 90

Age

CERAD male
CERAD female
McD&P male
McD&P female
Conclusions

- Rate of institutionalisation is age-related
- Mortality is generally higher than previously estimated post-onset
- Mortality from state 2 higher than from state 1
Need differential equations

- Kolmogorov forward equation
  \[
  \frac{\partial}{\partial t} p_x^{gh} = \sum_{j \neq h} (t p_x^{gj} \mu_{x+t}^{jh} - t p_x^{gh} \mu_{x+t}^{hj})
  \]

- Norberg’s equations for moments of present values
  \[
  \frac{\partial}{\partial t} V_t^{(q)j} = (q \delta_t^j + \mu_t^j) V_t^{(q)j} - q b_t^j V_t^{(q-1)j}
  \]
  \[
  - \sum \mu_t^{jk} \sum_{r=0}^{q} \binom{q}{r} (b_t^{jk})^r V_t^{(q-r)k}
  \]
Financial results

- Based on Macdonald & Pritchard in NAAJ 5 (2001)
- LTC benefit only while *in* State 3
- Benefit = $e^{\delta t}$
- 1st order Euler method
## Some expected costs

<table>
<thead>
<tr>
<th>State at start of contract</th>
<th>Entry Age</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>60</td>
<td>1</td>
<td>0.66</td>
<td>0.65</td>
<td>0.62</td>
<td>0.56</td>
<td>0.38</td>
<td>0.37</td>
</tr>
<tr>
<td>65</td>
<td></td>
<td>6.39</td>
<td>5.78</td>
<td>4.95</td>
<td>3.93</td>
<td>3.75</td>
<td>2.95</td>
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<tr>
<td>70</td>
<td></td>
<td>8.44</td>
<td>7.84</td>
<td>6.99</td>
<td>5.88</td>
<td>5.55</td>
<td>4.48</td>
</tr>
<tr>
<td>75</td>
<td></td>
<td>75</td>
<td>70</td>
<td>65</td>
<td>60</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>60</td>
<td>1</td>
<td>0.66</td>
<td>0.65</td>
<td>0.62</td>
<td>0.56</td>
<td>0.38</td>
<td>0.37</td>
</tr>
<tr>
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<tr>
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<td></td>
<td>8.44</td>
<td>7.84</td>
<td>6.99</td>
<td>5.88</td>
<td>5.55</td>
<td>4.48</td>
</tr>
<tr>
<td>75</td>
<td></td>
<td>75</td>
<td>70</td>
<td>65</td>
<td>60</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Medical interventions

- Current drugs
  - Donepezil
  - Galantamine
  - Rivastigmine
  - Memantine

- FDA-approved
- Available on NHS
- Treat symptoms only, not root cause

AChEi’s
Drug effects

- Results often reported as
  - Change in MMSE scores
  - Care-giver impact
  - Decrease in severity of symptoms
  - Adverse events
  - Sorted by mild, moderate and severe

- Nothing age-related
- Little re institutionalisation
Drug effects cont.

- No mortality effect
- Improved cognitive scores
- Occasional delayed NH admission
- Disputed results / effects
<table>
<thead>
<tr>
<th>Paper</th>
<th>Effect</th>
<th>Size (years)</th>
<th>Ave. (years)</th>
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<tbody>
<tr>
<td>Stewart</td>
<td>Delay in NH</td>
<td>0.2-0.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Jonsson</td>
<td>Longer in non-severe</td>
<td>0.5-0.8</td>
<td>0.65</td>
</tr>
<tr>
<td>O’Brien</td>
<td>Longer in non-severe</td>
<td>0.1-0.44</td>
<td>0.20</td>
</tr>
<tr>
<td>Hauber</td>
<td>Delay before severe</td>
<td>0.15-0.55</td>
<td>0.30</td>
</tr>
<tr>
<td>Getsios</td>
<td>5-10% longer pre-NH</td>
<td>0.25-0.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Garfield</td>
<td>10% reduction in FTC</td>
<td>0.3</td>
<td>0.30</td>
</tr>
<tr>
<td>AD2000</td>
<td>None</td>
<td></td>
<td>0.2??</td>
</tr>
</tbody>
</table>
Model & cost effects

- Female median age 75
- Constant hazard effect at all ages
- Find k such that

\[
\int_{0}^{\omega-x} (t) t p_x^{22} k \mu_{x+t}^{23} dt - \int_{0}^{\omega-x} (t) t p_x^{22} \mu_{x+t}^{23} dt = 0.33
\]

\[
K = 0.875
\]
## Cost effects of reduced $\mu^{23}$

<table>
<thead>
<tr>
<th>State at start of contract</th>
<th>% reduction</th>
<th>% reduction</th>
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<tr>
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<td>$K = 0.10$</td>
<td>$K = 0.30$</td>
</tr>
<tr>
<td></td>
<td>60 65 70 75</td>
<td>60 65 70 75</td>
</tr>
<tr>
<td>1</td>
<td>4.8 4.9 5.0 5.3</td>
<td>16.1 16.5 17.0 17.8</td>
</tr>
<tr>
<td>2</td>
<td>2.9 3.2 3.5 4.0</td>
<td>10.5 11.4 12.5 14.0</td>
</tr>
<tr>
<td>3</td>
<td>0.0 0.0 0.0 0.0</td>
<td>0.0 0.0 0.0 0.0</td>
</tr>
</tbody>
</table>
Position to-day

- NICE proposal to withdraw the AChEi drugs mainly on cost-effective grounds

- "For future studies, defining treatment response to AChEIs on the basis of clinically important outcomes, such as delay to institutionalization, maintenance of activities of daily living …… will clarify the benefits of these medications."

Lanctot et al (2001) CMAJ
Future medical treatments

- Amyloid cascade theory prevails
  - Plasma $\beta$ deposited as amyloid plaques
  - Various genetic, pathological and biochemical studies suggest that $\beta$ is not a marker but plays a causal role

- Suggests AD therapy based on altering $\beta$ accumulation
- Phase 2a clinical trial of AN-1792
- Withdrawn January 2002

7 new patents with Wyeth in last 12 months
Human autopsy case report #1: Reduction of cortical Aβ plaques after AN-1792 immunization

Amyloid plaque build-up in the brain is a hallmark of Alzheimer's disease. Research from clinical studies involving AN-1792 suggests evidence of amyloid plaque clearance in four autopsies. One case report is shown above.
Environmental factors

- Diet
  - Low in calories, cholesterol, saturated fats
- Cognitive stimulation
- Physical exercise
- Vitamin supplementation
- Potential for risk reduction like cardiovascular disease
Final Medical Word

Drugs to halt Alzheimer’s disease on the way

Ethne Donnellan, Health Correspondent

Drugs which will halt the progression of Alzheimer’s disease are likely to be available in less than a decade, a leading expert on the condition said in Dublin yesterday.

Prof Dennis Selkoe of Harvard Medical School, who has been studying the disease for 20 years, said it was “a tragedy” that there was no cure for Alzheimer’s disease.

“Most of the drugs that are being developed are aimed at delaying the progression of the disease,” he said.

Prof Selkoe added that the new “no-brainer” treatments will be available by 2010.

“People now who already have Alzheimer’s disease might benefit from this during the course of their illness,” he said.

“With a more likely beneficiary of this will be people about to get Alzheimer’s,” he said.

In Dublin for a conference on medical research into neuro-degenerative diseases at UCD, Prof Selkoe added that the new treatments “that make symptoms a little better but could not do anything about the progression of the disease”.

Alzheimer’s affects an estimated 35,000 people in Ireland but that figure is likely to increase dramatically in coming years as people live longer. In 95 per cent of cases the onset of the disease is after the age of 60 but there have been cases reported in people in their 40s.

The disease, Prof Selkoe said, was the eighth most frequent cause of death in the US in 1999, where there are about 4 million sufferers and where up to $100 billion a year is spent on treating sufferers.

“I have no doubt it would be very wise for the Irish public to invest its tax in research in figuring out this disease more quickly. “You could just let others do it but the...
Genetics review

- Early Onset AD
  - APP
  - PS-1
  - PS-1
- Late Onset AD
  - ApoE
APOE and ε4 allele

Farrer et al., 1997.
Other genes ??

- ε4 allele: 50% of LOAD
  - Lendon & Craddock (2001)
- Chromosome 10
  - Bertram et al (2001)
  - Tanzi et al (2001)
- A2M gene (Ch 12)
- 4 loci >ApoE & ApoE = 10%
Other genes??

- ApoE genotype = 95%

- No one single gene
  - Perhaps many genes of small effect

- Years for useful volume of data??
Further work

- Other data sets
- MMSE-based model with extra state
- Onset by sex
- ApoE prospective studies?
- Watching brief on therapies
- What if questions
  - e.g. remove excess ε4 risk
Advice 1

Calculus and alcohol don’t mix

Or

Don't drink and derive!
Advice 2

Be careful what you wish for
It just might come true!!!