Here’s the thing about Dementia

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Consulting Medical Officer Gen Re
Consultant Psychiatrist
South London and Maudsley Trust
Projected increase in people with dementia in UK

Economic impact of dementia

Overall impact £26.3 billion

£4.3 billion on healthcare
£85 million on diagnostics

£10.3 billion on social care
£4.5 billion publically funded
£5.8 billion privately funded

Unpaid care £11.6 billion (44% of cost)

Public LTC Expenditure as a Share of GDP

Source: OECD calculations and 2000 Ageing Report, European Union
Rhetoric and Dementia

It’s a fact that Alzheimer’s Disease is an escalating epidemic.

The number of Americans with Alzheimer's Disease and other dementias will grow each year as the size and proportion of the U.S. population age 65-and-older continue to increase. By 2050, the number of people with Alzheimer’s may rise as high as 16 million (8/4/15)
Cautions

Western estimates made on studies from the 1980s

UK - aged 65+ - 24% decline in prevalence in 2011 than was predicted in 1990

Spain - men + decline of 43% between 1987 and 1996

Main reason - decline of cardiovascular disease and its risk factors

Improvements in living conditions and education

Cautions

Western estimates made on studies from the 1980s

UK - aged 65+ - 22% decline in prevalence in 2011 than was predicted in 1990

Spain - men + decline of 43% between 1987 and 1996

Main reason - decline of cardiovascular disease and its risk factors
Improvements in living conditions and education

Framingham

Compared to the first epoch
Second -22%
Third -38%
Fourth -44%
(hazard ratio, 0.77; 95% confidence interval, 0.67 to 0.88).

Incidence of Dementia over Three Decades in the Framingham Heart Study

20% drop in incidence (95% CI: 0–40%),
Driven by a reduction in men across all ages above 65
40,000 fewer cases than estimates two decades ago would suggest

Nature Communications Volume: 7, Article number: 11398 DOI:doi:10.1038/ncomms11398
Modifiable Risk Factors

Obesity
Low educational achievement
Depression
Hypertension
Frailty
Smoking
Type 2 Diabetes

Population attributable risk of 66%

Meta-analysis of modifiable risk factors for Alzheimer's disease
J Neurol Neurosurg Psychiatry doi:10.1136/jnnp-2015-310548

http://jnnp.bmj.com/content/early/2015/07/27/jnnp-2015-310548
# Modifiable Risk Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>1.39</td>
</tr>
<tr>
<td>Midlife Hypertension (untreated)</td>
<td>1.61</td>
</tr>
<tr>
<td>Midlife Obesity (BMI&gt;=30)</td>
<td>1.60</td>
</tr>
<tr>
<td>Depression</td>
<td>1.90</td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td>1.82</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.59</td>
</tr>
<tr>
<td>Cognitive inactivity or low educational attainment</td>
<td>1.59</td>
</tr>
</tbody>
</table>

Modifiable Risk Factors: Diabetes

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2040</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia cases prevented:</td>
<td>23,100</td>
<td>40,000</td>
</tr>
<tr>
<td>Life years saved:</td>
<td>92,700</td>
<td>149,700</td>
</tr>
<tr>
<td>Total savings (for the state):</td>
<td>£321m</td>
<td>£560m</td>
</tr>
</tbody>
</table>

Potential Savings (2013) - Total: £661m. Of which government savings are: £321m

# Dementia and Survival

<table>
<thead>
<tr>
<th>Age</th>
<th>Women</th>
<th>Women + Dementia</th>
<th>Men</th>
<th>Men + dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-64</td>
<td>25.07</td>
<td>9.4</td>
<td>22.3</td>
<td>7.4</td>
</tr>
<tr>
<td>65-69</td>
<td>20.8</td>
<td>7.5</td>
<td>18.3</td>
<td>5.9</td>
</tr>
<tr>
<td>70-79</td>
<td>16.7</td>
<td>5.8</td>
<td>14.5</td>
<td>4.5</td>
</tr>
<tr>
<td>80-89</td>
<td>9.6</td>
<td>4.4</td>
<td>8.2</td>
<td>3.7</td>
</tr>
<tr>
<td>90+</td>
<td>4.6</td>
<td>3.9</td>
<td>4.2</td>
<td>3.4</td>
</tr>
</tbody>
</table>

After OHE 2014 + National Life Tables


Source: Office for National Statistics licensed under Open Government Licence v.3.0
Dementia Symptoms

Memory loss - recent events, messages, names
Difficulties organising and planning activities
Confusion in unfamiliar environments
Difficulty finding words
Difficulty with numbers and/or handling money
Changes in personality and mood
Depression

Dementia Definition

Acquired, progressive and abnormal deterioration of memory, and at least one other area of cognitive function, which is affecting the daily life of the person, and not due to affective disorders or delirium (Rees, Lipsedge & Ball 1996)

Dementia is a syndrome (essentially brain failure) affecting higher functions of the brain (Barrett & Burns 2014)

There are many causes of Dementia
<table>
<thead>
<tr>
<th>Type</th>
<th>Female</th>
<th>Male</th>
<th>Both</th>
<th>Numbers of people with dementia (rounded figures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>66.2%</td>
<td>54.6%</td>
<td>62.3%</td>
<td>475,000</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>14.8%</td>
<td>20.5%</td>
<td>16.7%</td>
<td>130,000</td>
</tr>
<tr>
<td>Mixed (AD &amp; VD)</td>
<td>10.2%</td>
<td>10.9%</td>
<td>10.4%</td>
<td>77,000</td>
</tr>
<tr>
<td>Lewy bodies dementia</td>
<td>2.7%</td>
<td>5.6%</td>
<td>3.8%</td>
<td>31,000</td>
</tr>
<tr>
<td>Fronto-temporal dementia</td>
<td>1.4%</td>
<td>2.3%</td>
<td>1.7%</td>
<td>15,000</td>
</tr>
<tr>
<td>Parkinsons</td>
<td>1.3%</td>
<td>2.7%</td>
<td>1.7%</td>
<td>15,000</td>
</tr>
<tr>
<td>Other</td>
<td>3.5%</td>
<td>3.5%</td>
<td>3.5%</td>
<td>27,000</td>
</tr>
</tbody>
</table>

Not ‘just your age dear’

Prevalence Men  Prevalence Women

Normal Aging
Everyone experiences slight cognitive changes during aging

Preclinical
- Silent phase: brain changes without measurable symptoms
- Individual may notice changes, but not detectable on tests
- “A stage where the patient knows, but the doctor doesn’t”

MCI
- Cognitive changes are of concern to individual and/or family
- One or more cognitive domains impaired significantly
- Preserved activities of daily living

Dementia
- Cognitive impairment severe enough to interfere with everyday abilities
- Severe
- Moderately Severe
- Moderate
- Mild

https://www.mind.uci.edu/alzheimers-disease/what-is-alzheimers/mild-cognitive-impairment/
What makes Alzheimer’s Disease, Alzheimer’s Disease?

Tangles - made of Tau

Plaques – made of Amyloid

http://petridishtalk.com/2011/05/
Amyloid Cascade Hypothesis

Accumulation of amyloid triggers neuronal degeneration

Accumulation triggers cell death

Amyloid interferes with mitochondrial function

Amyloid interferes with neurotransmitters and glucose use

Failure to develop treatments

Trial design

Excessive side-effects biased enrolment

Heterogeneity of the AD process

No linear relationship between amyloid and cognition

No amyloid cognitive impairment (20%)

Too late and/or the wrong target

DOI: 10.1002/ana.24227
Biomarkers and embodying risk

‘(Genetic) technologies permit us to speculate with much greater precision than was formerly the case about who may be struck by misfortune…’

Amyloid PET

Cerebrospinal fluid

**Amyloid-beta(1-42):**
Reduction amyloid-beta

**Total Tau:**
Increase in Total Tau
Total Tau predicts conversion of MCI

**Phosphorylated Tau:**
Phosphorylated Tau distinguishes AD from other conditions
Low AB42 and Low Tau
Low AB42 and Intermediate Tau
Low AB42 and High Tau


https://www.genevaassociation.org/media/58196/ga_ed_382_10_smalley_health,dementia,underwriting.pdf
Genetics: **Early** Onset Alzheimer’s Disease

**Presenillin 1**  
Early age of onset – 15% Familial cases

**Presenillin 2**  
Later onset and not all progress to dementia

**Amyloid Precursor Gene (APP)**  
Together fewer than 1 in 100 cases

Excess production of Amyloid

Genetics: Late Onset Alzheimer’s Disease

APOE gene - Identified in 1983
Three common forms e 2, 3 and 4
5 common genotypes 2/3, 3/3, 2/4, 3/4, 4/4
e4 present in 25-30% population
e4/4 variant 10 times the risk
Not everyone with e4 develops the disease
Between 1/3 and ½ of those with LOAD do not have e4
Genetics: **Late** Onset Alzheimer’s Disease

http://gladstoneinstitutes.org/node/11431
Age at which 15% of people were accumulating amyloid by APOE status


<table>
<thead>
<tr>
<th>Apo E Status</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/4</td>
<td>40</td>
</tr>
<tr>
<td>2/4</td>
<td>50</td>
</tr>
<tr>
<td>3/4</td>
<td>55</td>
</tr>
<tr>
<td>3/3</td>
<td>65</td>
</tr>
<tr>
<td>2/3</td>
<td>95</td>
</tr>
</tbody>
</table>
The price to sequence the entire human genome has dropped from $3 billion to $60,000.

Genome Wide Association Studies

Strongest evidence for APOE involvement

Complex interaction between multiple genes

Epigenetics

The expression of these genes depends on interaction with the environment

Potential to alter the expression of these genes
Genome Wide Association Studies

Cholesterol Metabolism
- APOE, SORL1, CLU, ABCA7

Endocytosis
- PICALM, SORL1, CD2AP, BIN1

Amyloid Cascade

LOAD

AD

FAD

Amyloid Cascade
- APP SEN1 SEN2

Immunity
- INPP5D, EPHA1, HLA, CR1, MSA4, TREM2/TREML2

Unknown
- NME8, CASS4, ZCWPW1, FERMT2, PTK2B, MEF2C, CELF1, SLC24A4

95% 5%

Blood

Easily accessible but not in contact with the brain

Blood is a complex fluid

Single molecule studies not useful

Proteomics – Identify a protein signature for a disease

Potentially a cheap and acceptable biomarker for presymptomatic AD
Proteomics

Replication studies inconsistent e.g. Kiddle et al (2014)

Non-specific e.g Chiam et al (2015)

But quite exciting  Hye et al (2014)
Ideal Biomarker

Sensitive and specific

Identifies pathological process before clinical symptoms

Can be used for screening

Is proportionate to the severity of that process

Can be used as a marker for therapy

Cheap, acceptable
What does this mean for insurance?


Overview

• Earlier diagnosis via biomarkers
  - Impact on Critical Illness
  - Potential for future treatments and mortality improvements

• Genetic predisposition
  - US studies on APOE genes and LTC insurance decisions
  - Estimate of price distinction by APOE genotype for UK insurance products
Critical Illness definition of Alzheimer’s Disease and Dementia

**Alzheimer’s disease [before age x] – resulting in permanent symptoms**

A definite diagnosis of Alzheimer’s disease [before age x] by a Consultant Neurologist, Psychiatrist or Geriatrician. There must be permanent clinical loss of the ability to do all of the following:

- remember;
- reason; and
- perceive, understand, express and give effect to ideas.

For the above definition, the following are not covered:
- Other types of dementia.

**Dementia – resulting in permanent symptoms**

A definite diagnosis of dementia by a Consultant Neurologist, Psychiatrist or Geriatrician. There must be permanent clinical loss of the ability to do all of the following:

- remember;
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Effect of earlier diagnosis on dementia incidence

Comparison of current and possible early diagnosis dementia incidence with cancer incidence

Sources:
Effect of earlier diagnosis on dementia incidence

Comparison of current and possible early diagnosis dementia incidence with cancer incidence

Sources are own calculations based on:
Mortality trends – Dementia deaths as a % of total

In January 2011, ONS introduced a new version of ICD-10. This change affected cause of death coding.

Vascular dementia was previously assigned to cerebrovascular disease.

A number of dementia deaths were previously coded as urinary tract infection, site not specified or bronchopneumonia.

Dementia as primary cause of death as a % of total by age band: Males

Dementia as primary cause of death as a % of total by age band: Females

If dementia deaths were shifted 5 years later between 2001 and 2010, mortality rates in 2010 would have been 3 - 4.5% lower for 75 – 79 year olds and 5% to 7.5% lower for ages 80 - 84.

Alzheimer’s Disease Genes: Insurance Case studies from the US
Genetic testing and insurance purchasing decisions: background

Taylor et al, Genetic Testing For Alzheimer’s And Long-Term Care Insurance, *Health Affairs* 29, no.1 (2010):102-108

- The Piedmont Health Survey of the Elderly:
  - Community-based study in North Carolina
  - Almost 2000 subjects aged 65+
  - Used APOE genotype as a predictor of moving to a nursing home
  - Study inception 1986/87 with follow-up until 31 December 2006

- REVEAL II study:
  - 276 first degree relatives of people with Alzheimer’s disease, mean age 58.
  - Subjects provided with education and APOE genotyping
  - Compared LTC insurance arrangements at baseline and at 1-year follow-up

- Rotterdam study:

- Genetic Information Nondiscrimination Act (GINA) of 2008:
  - Illegal for health insurers and employers to discriminate based on the results of genetic testing.
  - Does not affect long-term care, disability, or life insurance in all States

http://gladstoneinstitutes.org/node/11431
Odds ratios for subjects with at least one e4 APOE allele vs 2 e3 alleles

- Nursing home admission: **1.48** 95% CI 1.09; 2.01 (Piedmont Study)
- Developing Alzheimer’s Disease: **4.6** 95% CI 1.3; 16.1 (Rotterdam Study)
- Changing LTC insurance: **2.31** 95% CI 1.11; 4.81 (REVEAL II Study)
Mortality differentials by APOE genotype

- The APOE e4 allele is associated with an elevated risk of death, including non-Alzheimer’s Disease deaths

Source:
Products where APOE genotype could be useful underwriting information

Significant value for:

- Pre-funded LTC negligible (vs US <10% of population): **+50% rating for one APOE e4 allele**
- Mortality Term / WOL Assurance **+25% to +50% rating for e3/4 APOE allele, double this for e4/4 allele**
- (Enhanced/Impaired) guaranteed income for life

Limited value for:

- Critical Illness
- Income Protection

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