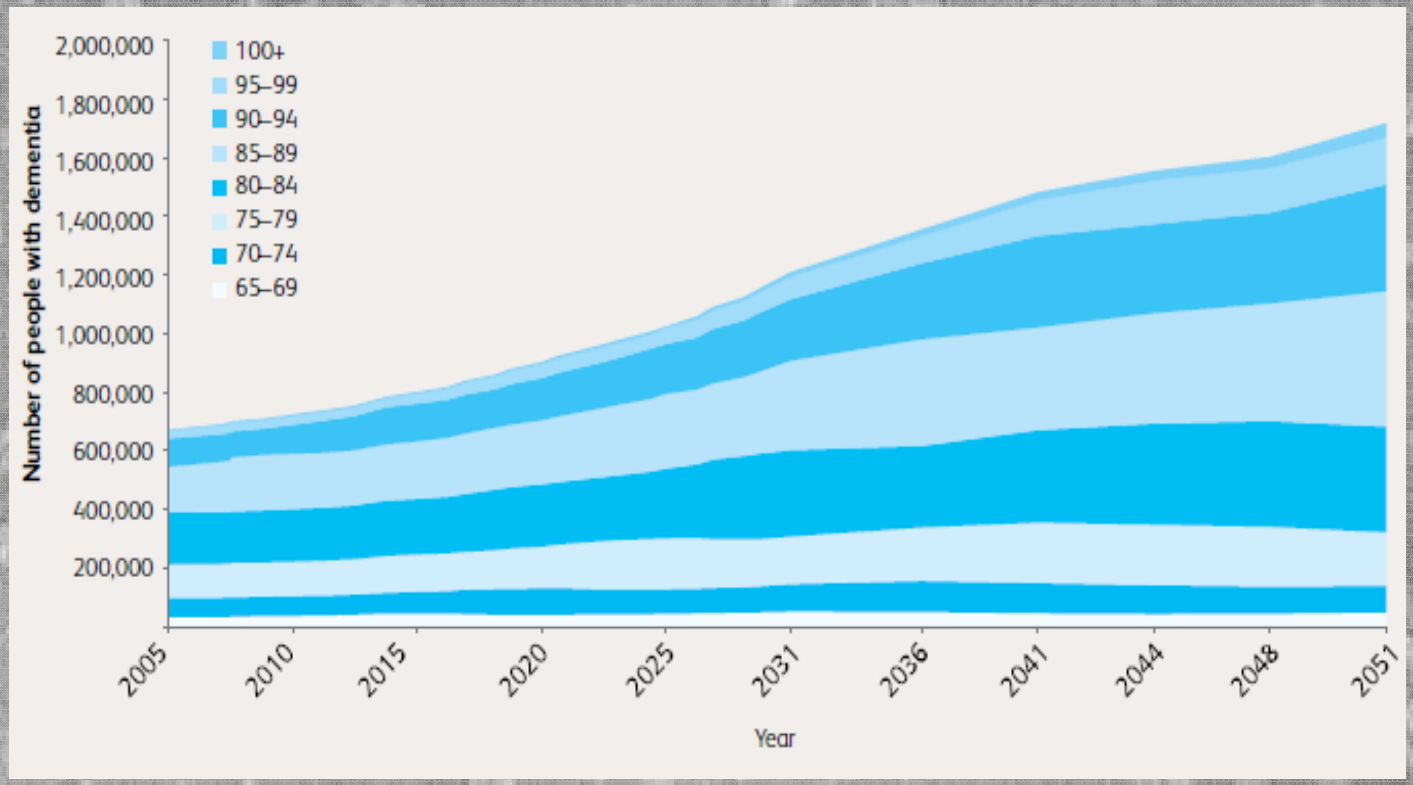
Here's the thing about Dementia

Dr Chris Ball MRCPsych
Consulting Medical Officer Gen Re
Consultant Psychiatrist
South London and Maudsley Trust



Projected increase in people with dementia in UK

https://www.alzheimers.org.uk/site/scripts/download_info.php?fileID=2323

Economic impact of dementia

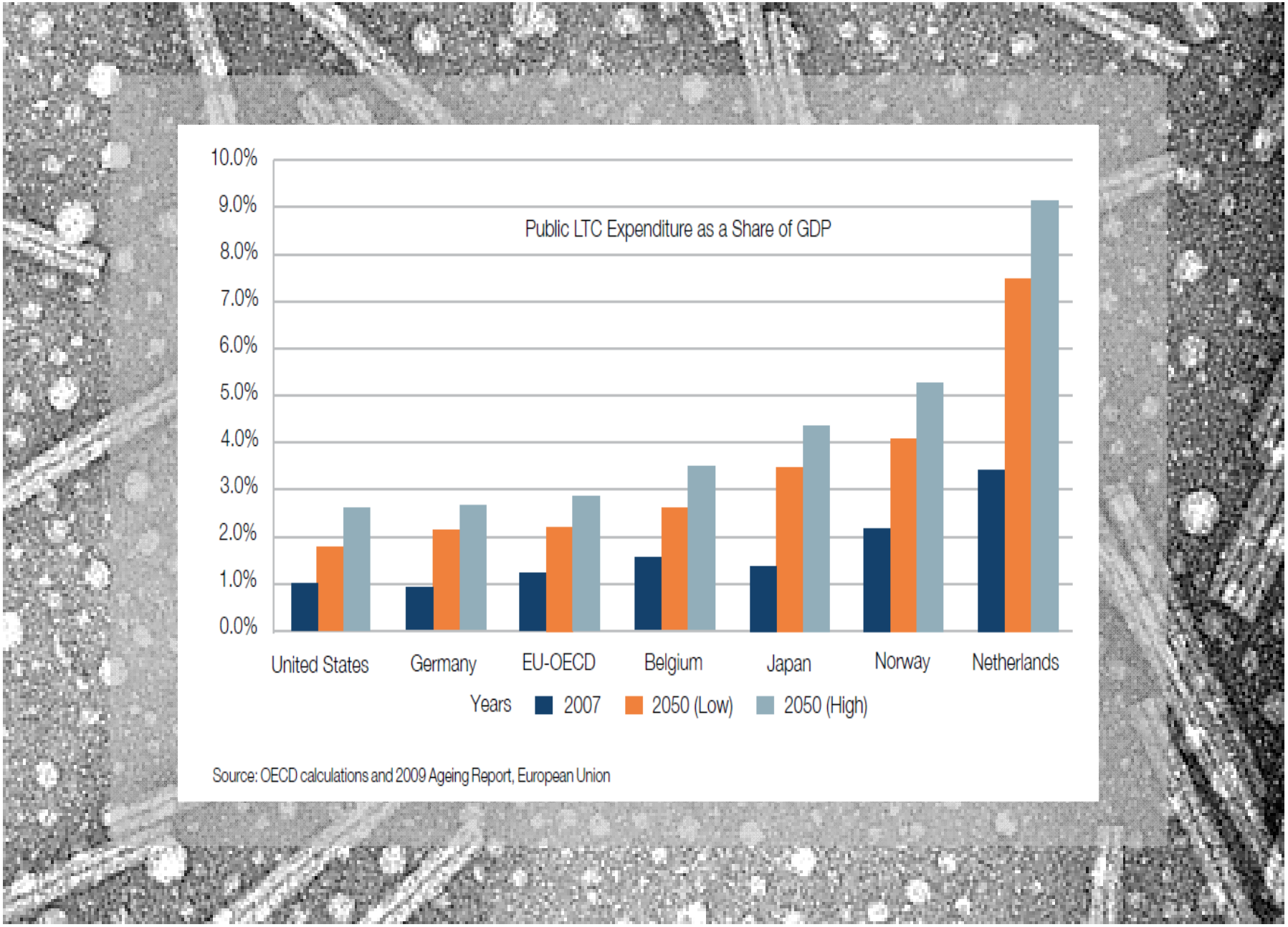
Overall impact £26.3 billion

£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)

https://www.alzheimers.org.uk/site/scripts/download_info.php?fileID=2323


Public LTC Expenditure as a Share of GDP
10.0%
9.0%
8.0%
7.0%
6.0%
5.0%
4.0%
3.0%
2.0%
1.0%
0.0%
United States
Germany
EU-OECD
Belgium
Japan
Norway
Netherlands
Years
2007
2050 (Low)
2050 (High)
Source: OECD calculations and 2009 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

http://www.medscape.com/viewarticle/850437

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

http://www.medscape.com/viewarticle/850437

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
Satizabal, N Engl J Med 2016; 374:523-532

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

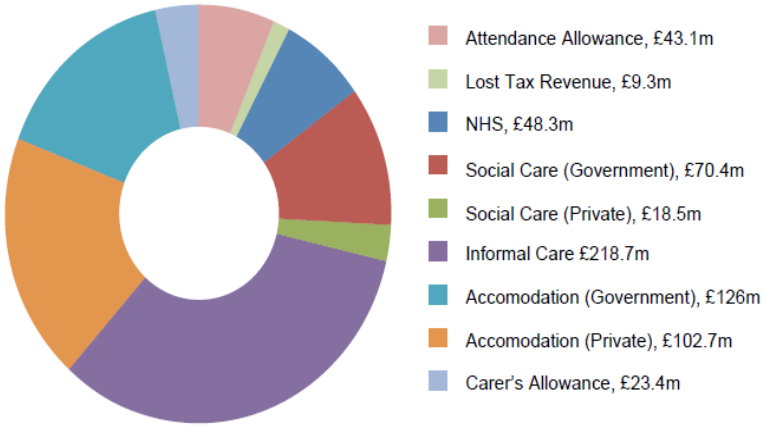
Risk factor	Relative risk (RR)
Diabetes mellitus	1.39
Midlife Hypertension (untreated)	1.61
Midlife Obesity (BMI>=30)	1.60
Depression	1.90
Physical Inactivity	1.82
Smoking	1.59
Cognitive inactivity or low educational attainment	1.59

http://www.ilcuk.org.uk/images/uploads/publication-pdfs/ILC_Dementia_and_Prevention.pdf

Modifiable Risk Factors: Diabetes

	2013	2040
Dementia cases prevented:	23,100	40,000
Life years saved:	92,700	149,700
Total savings (for the state):	£321m	£560m

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



http://www.ilcuk.org.uk/images/uploads/publication-pdfs/ILC_Dementia_and_Prevention.pdf

Dementia and Survival

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

After OHE 2014 + National Life Tables

http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-365199

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

http://www.nhs.uk/conditions/dementia-guide/pages/symptoms-of-dementia.aspx

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)

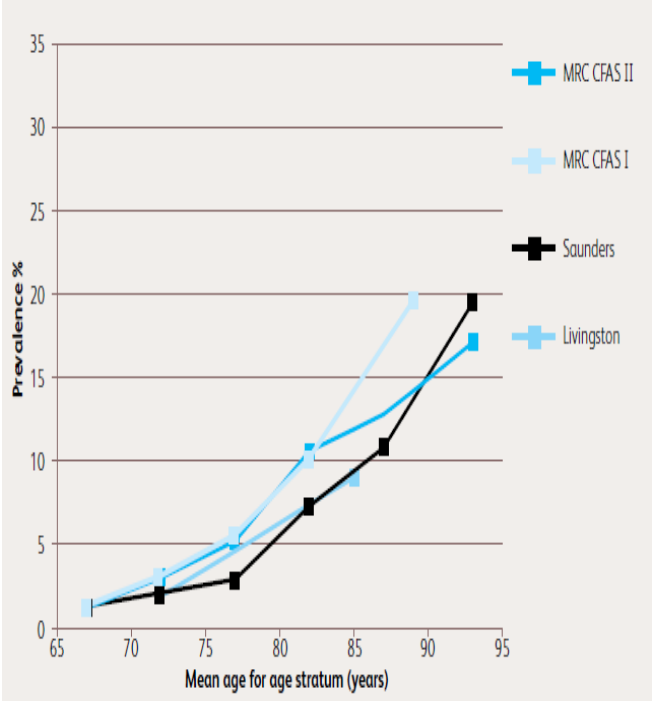
There are many causes of Dementia

Type	Percentage of all people with dementia (rounded figures)			Numbers of people with dementia (rounded figures)
	Female	Male	Both	
Alzheimer's disease	66.2%	54.6%	62.3%	475,000
Vascular dementia	14.8%	20.5%	16.7%	130,000
Mixed (AD & VD)	10.2%	10.9%	10.4%	77,000
Lewy bodies dementia	2.7%	5.6%	3.8%	31,000
Fronto-temporal dementia	1.4%	2.3%	1.7%	15,000
Parkinsons	1.3%	2.7%	1.7%	15,000
Other	3.5%	3.5%	3.5%	27,000

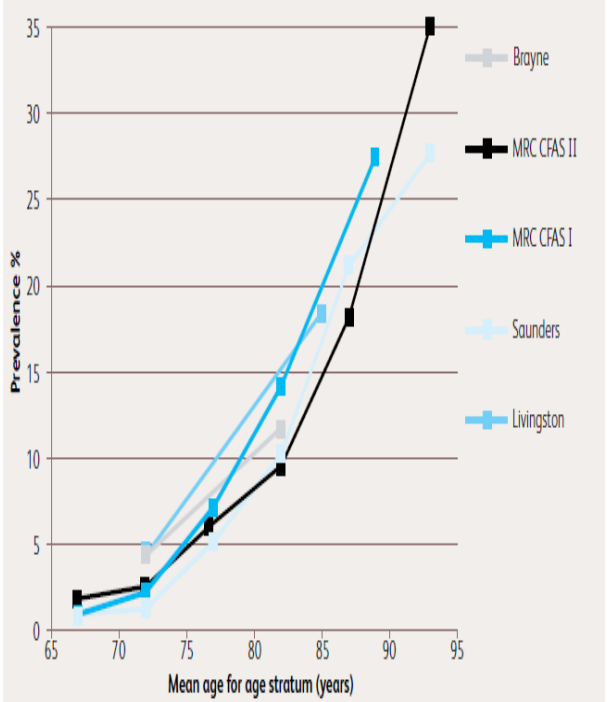
http://www.ilcuk.org.uk/images/uploads/publication-pdfs/ILC_Dementia_and_Prevention.pdf

Not ‘just your age dear’

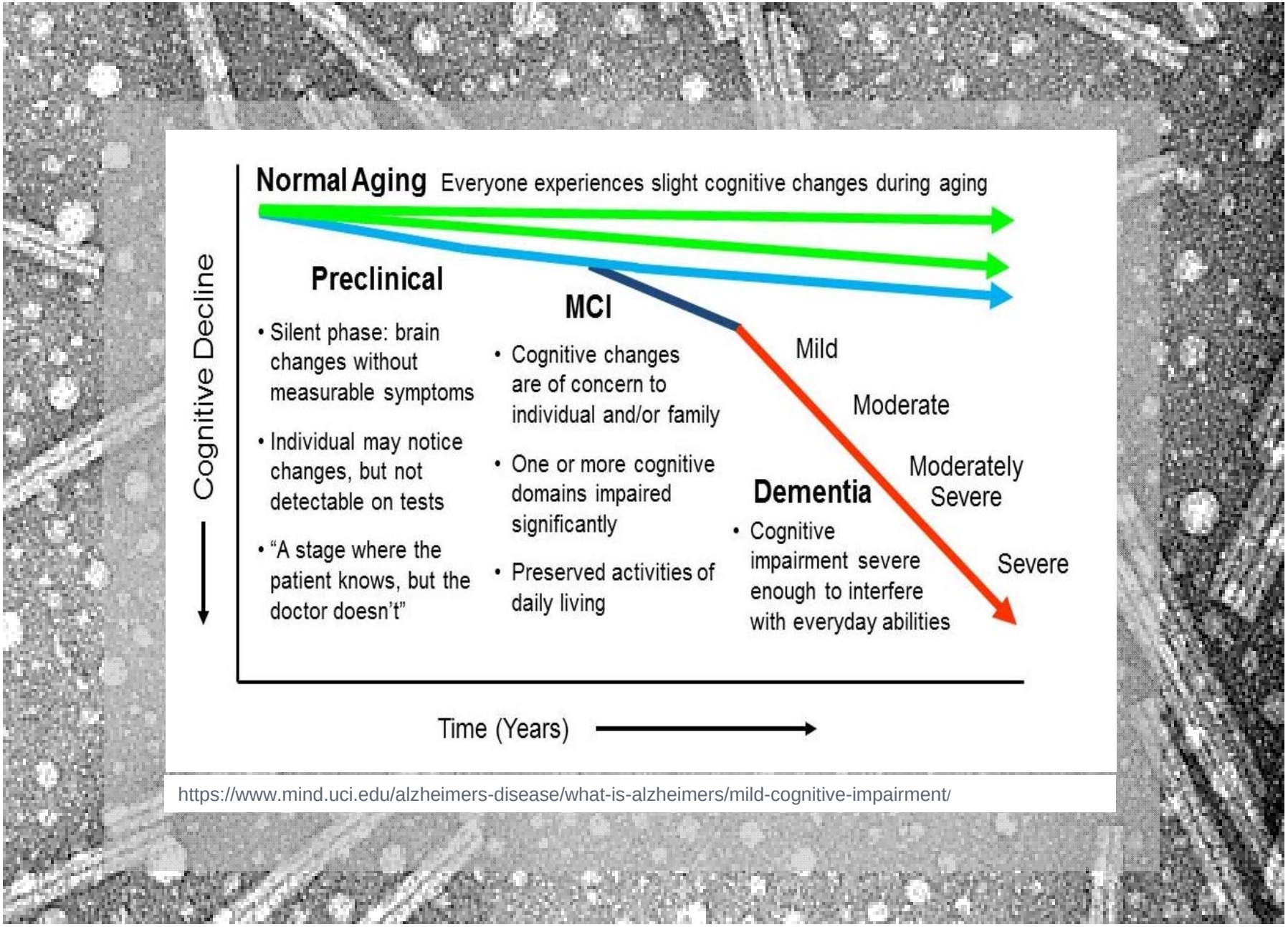
Prevalence Men



Prevalence Women



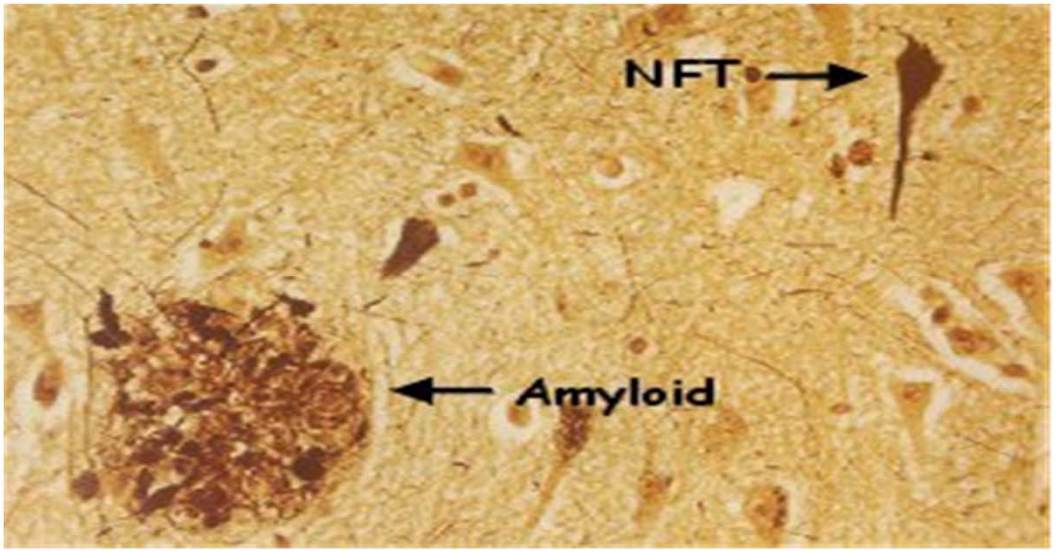
https://www.alzheimers.org.uk/site/scripts/download_info.php?fileID=2323



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

http://www.medscape.org/viewarticle/769590_slide

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%)

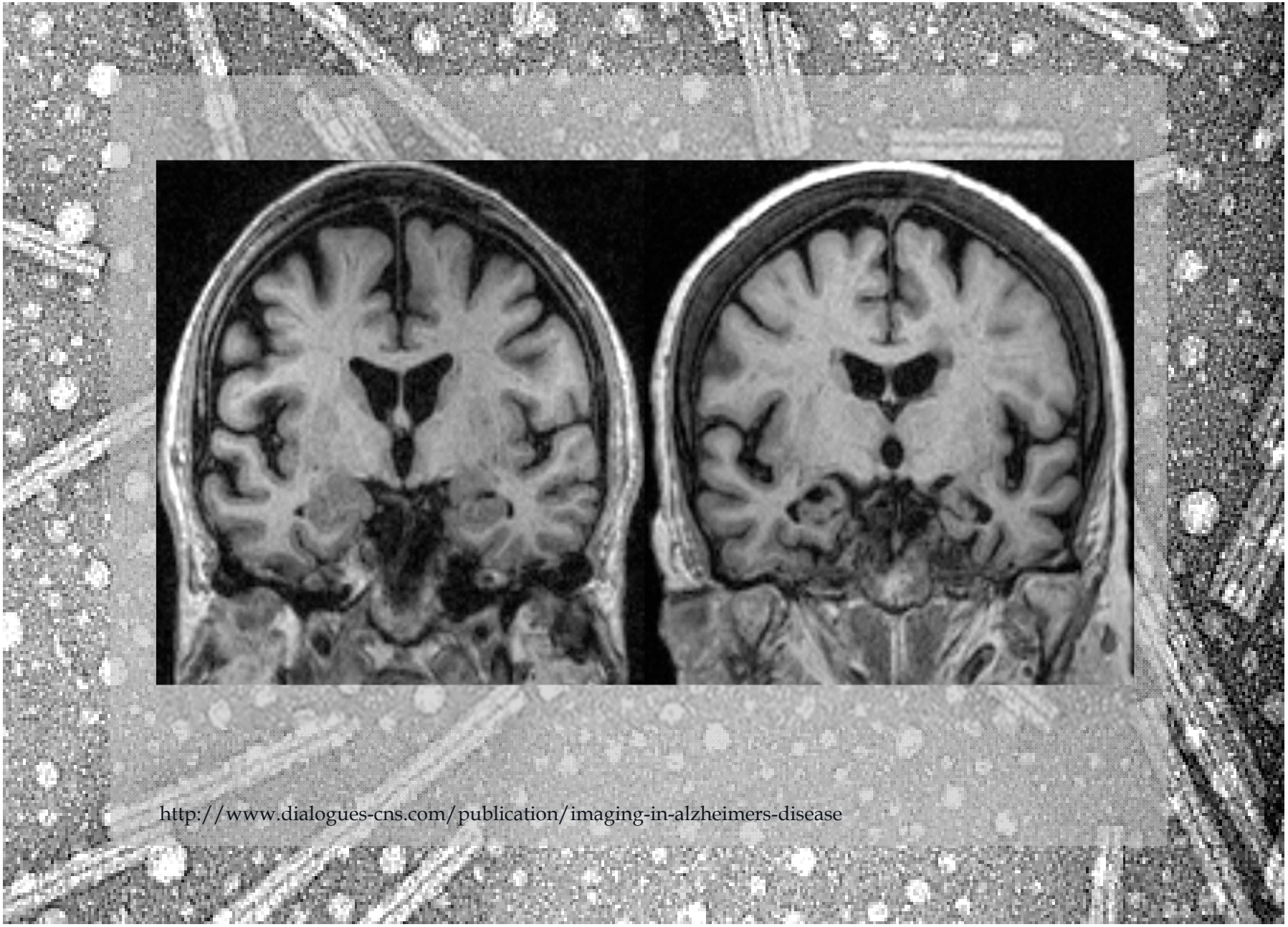
Too late and/or the wrong target

DOI: 10.1002/ana.24227

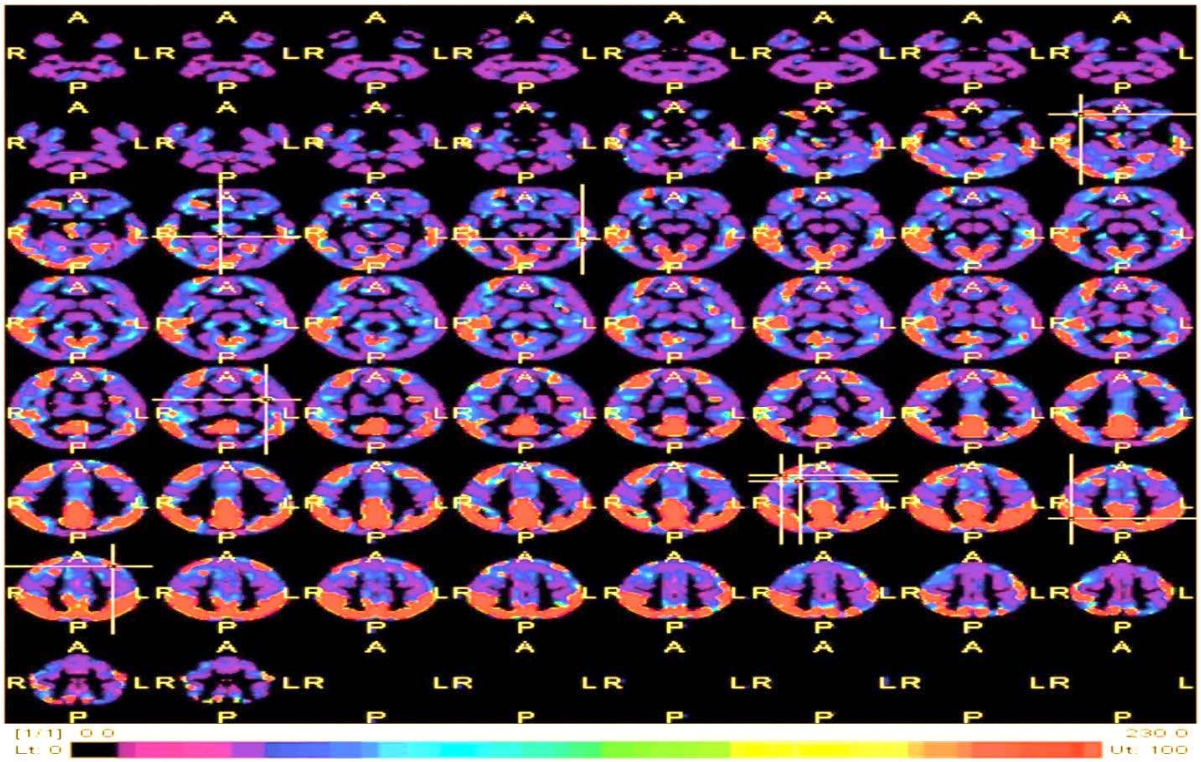
Biomarkers and embodying risk

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

Lock, M. (2013) The Alzheimer’s Conundrum.

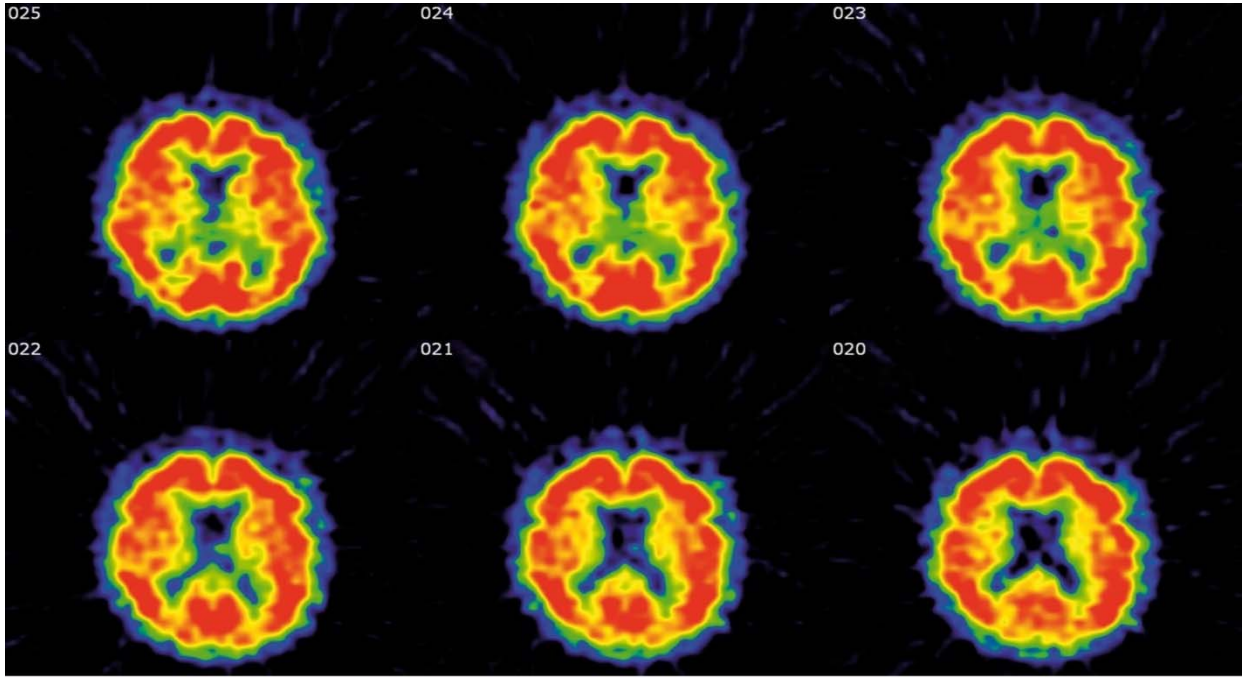


http://www.dialogues-cns.com/publication/imaging-in-alzheimers-disease



http://www.dialogues-cns.com/publication/imaging-in-alzheimers-disease

Amyloid PET



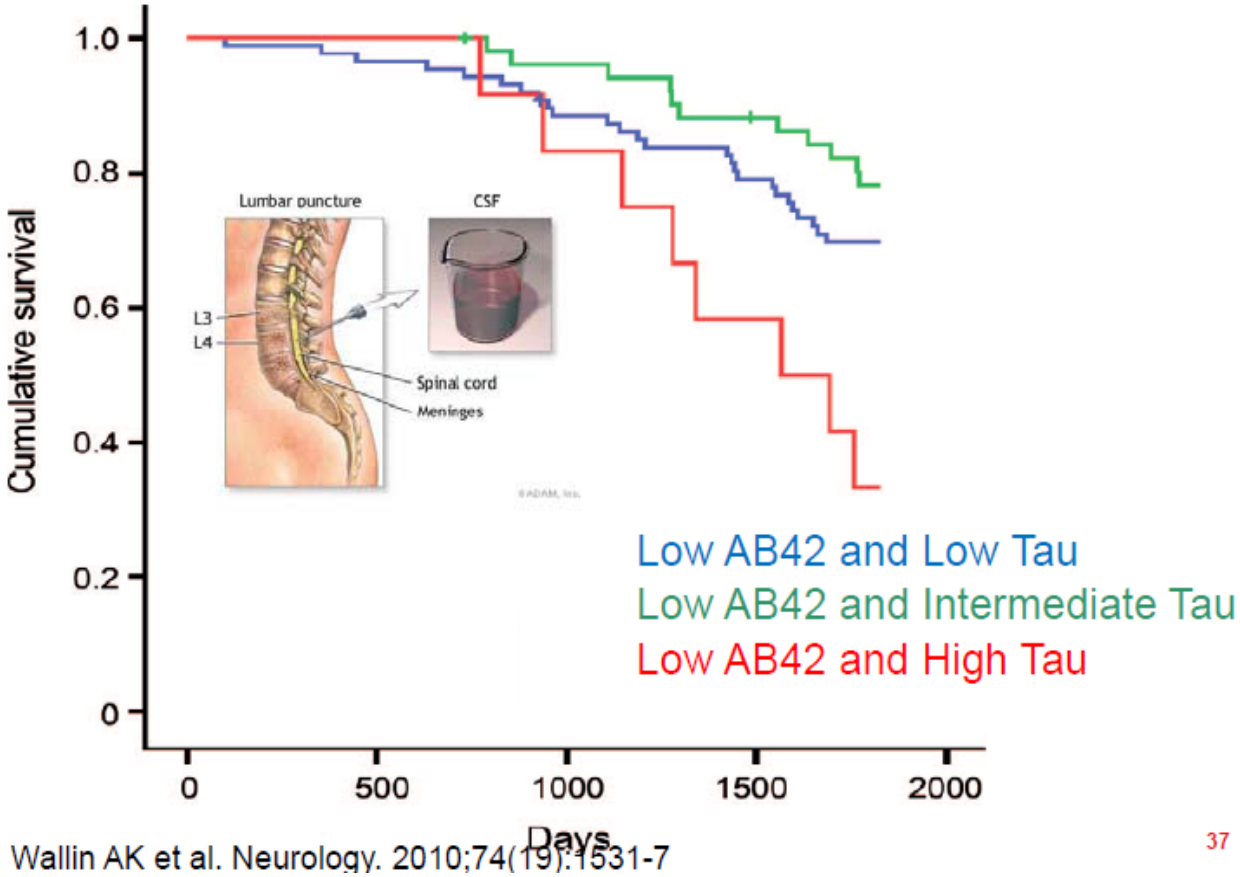
http://www.dialogues-cns.com/publication/imaging-in-alzheimers-disease

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



Wallin AK et al. Neurology. 2010;74(19):1531-7

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 Precurser Gene (APP)

Together fewer than 1 in 100 cases

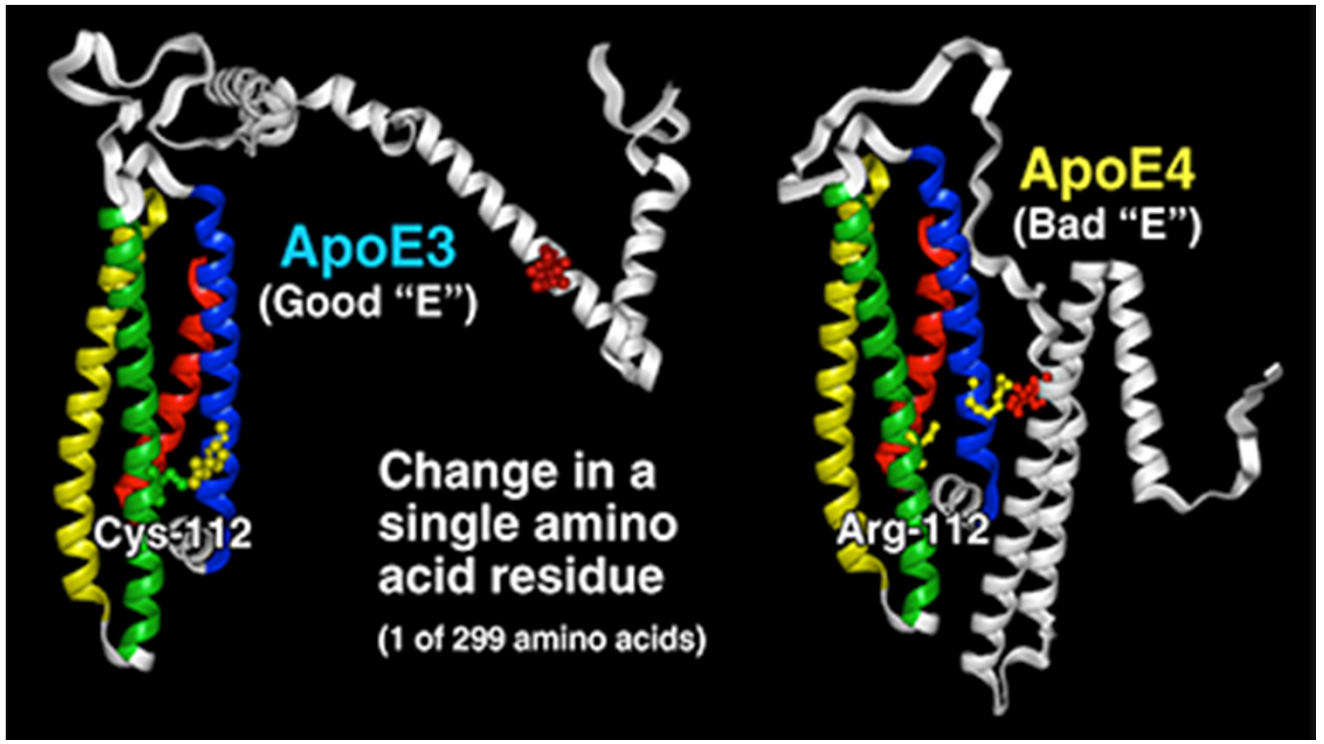
Excess production of Amyloid

Lock, M. (2013) The Alzheimer Conundrum

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

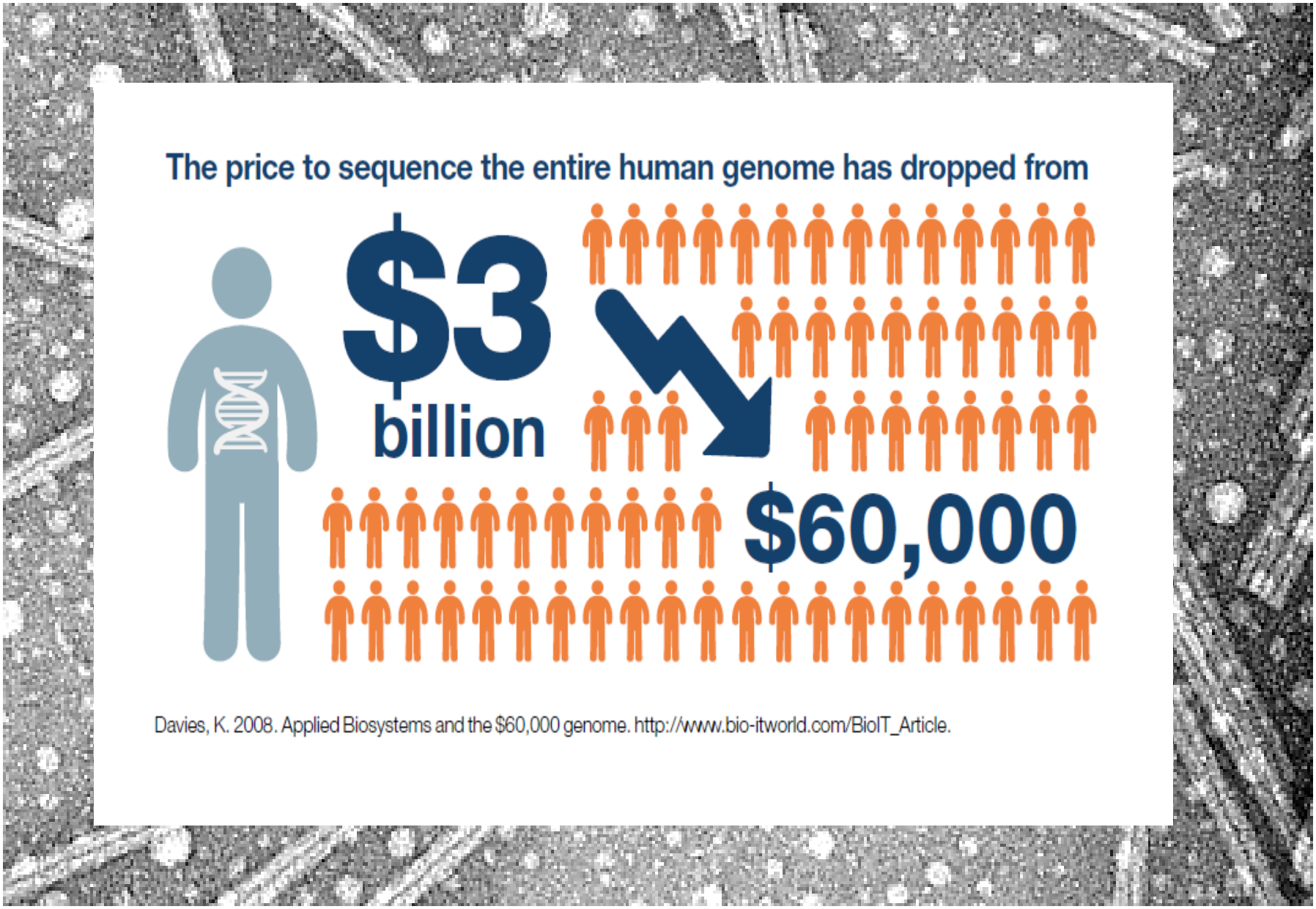


http://gladstoneinstitutes.org/node/11431

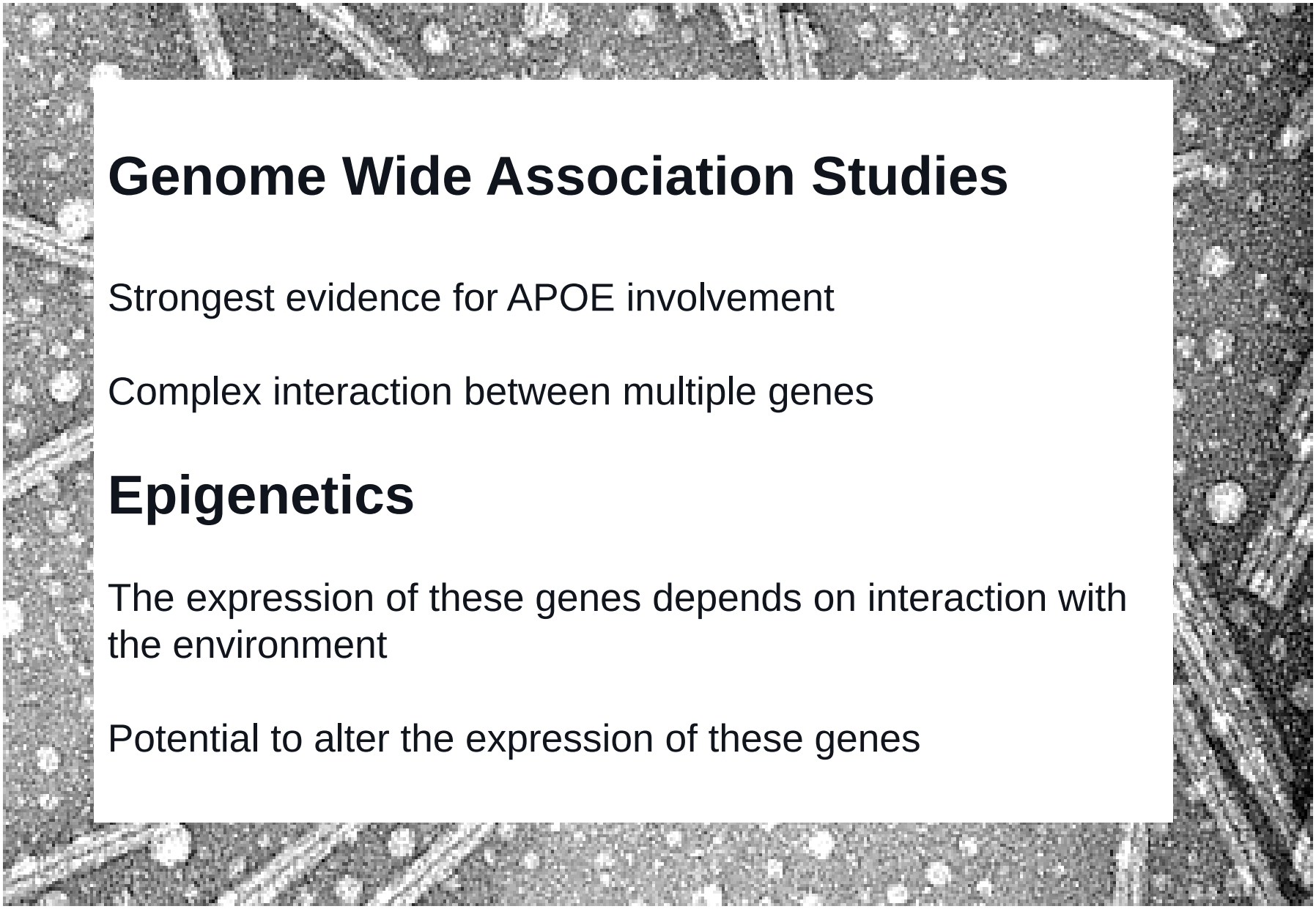
Apo E Status	Age
4/4	40
2/4	50
3/4	55
3/3	65
2/3	95

Age at which 15% of people were accumulating amyloid by APOE status

JAMA. 2015;313(19):1924-1938. oi:10.1001/jama.2015.4668



Davies, K. 2008. Applied Biosystems and the $60,000 genome. http://www.bio-itworld.com/BioIT_Article.



Genome Wide Association Studies

Strongest evidence for APOE involvement

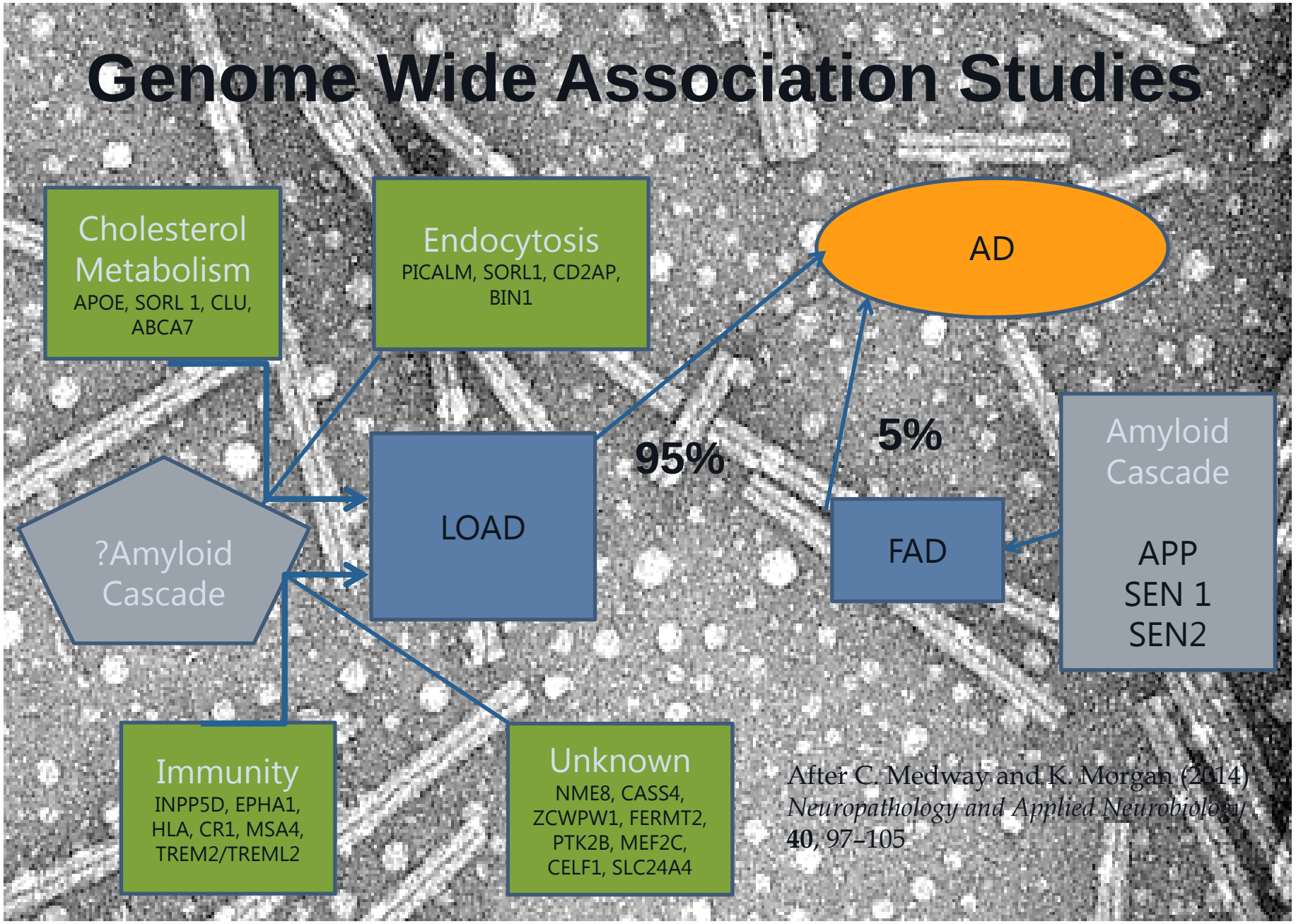
Complex interaction between multiple genes

Epigenetics

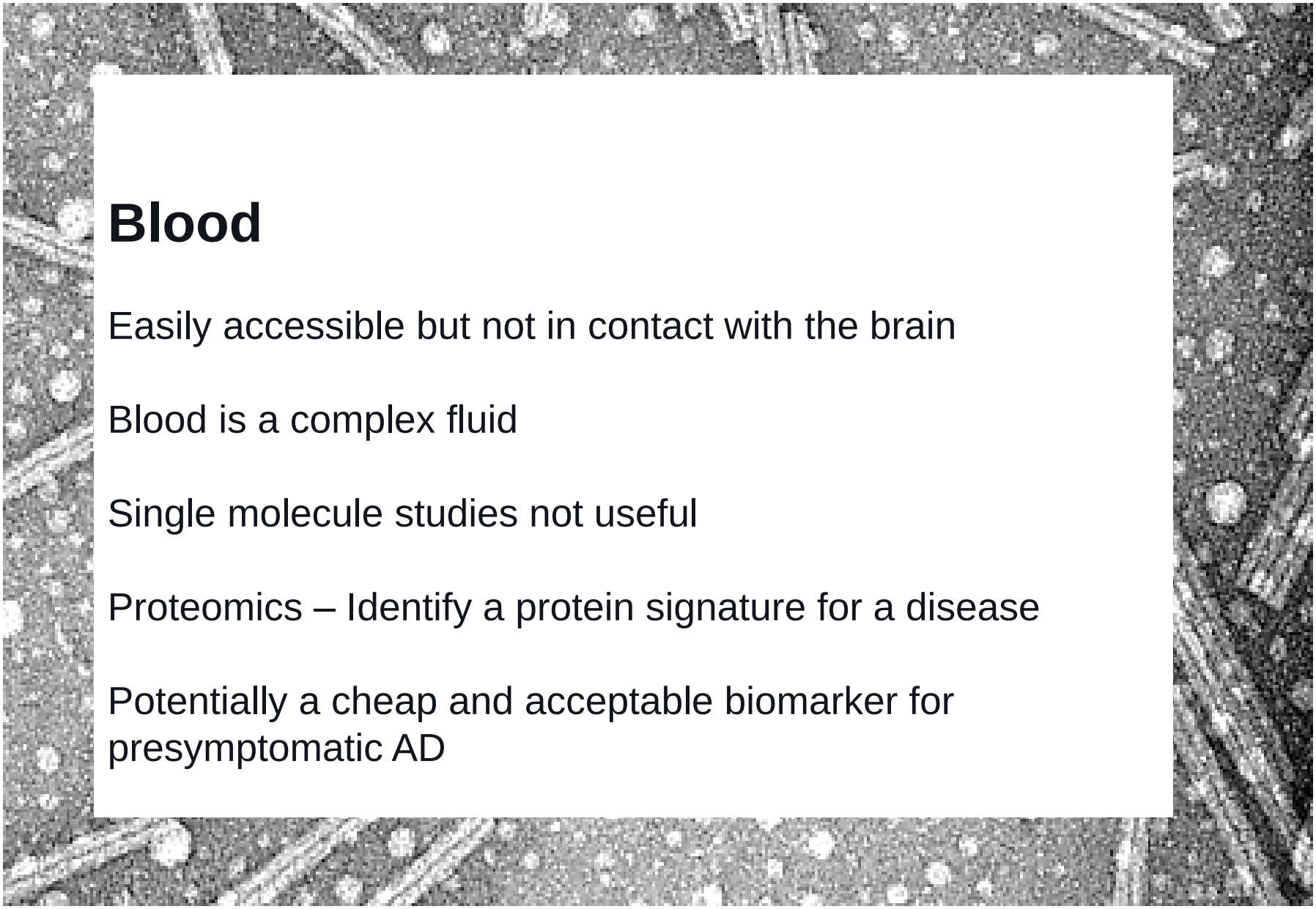
The expression of these genes depends on interaction with the environment

Potential to alter the expression of these genes

Genome Wide Association Studies



After C. Medway and K. Morgan (2014) *Neuropathology and Applied Neurobiology* **40**, 97–105



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

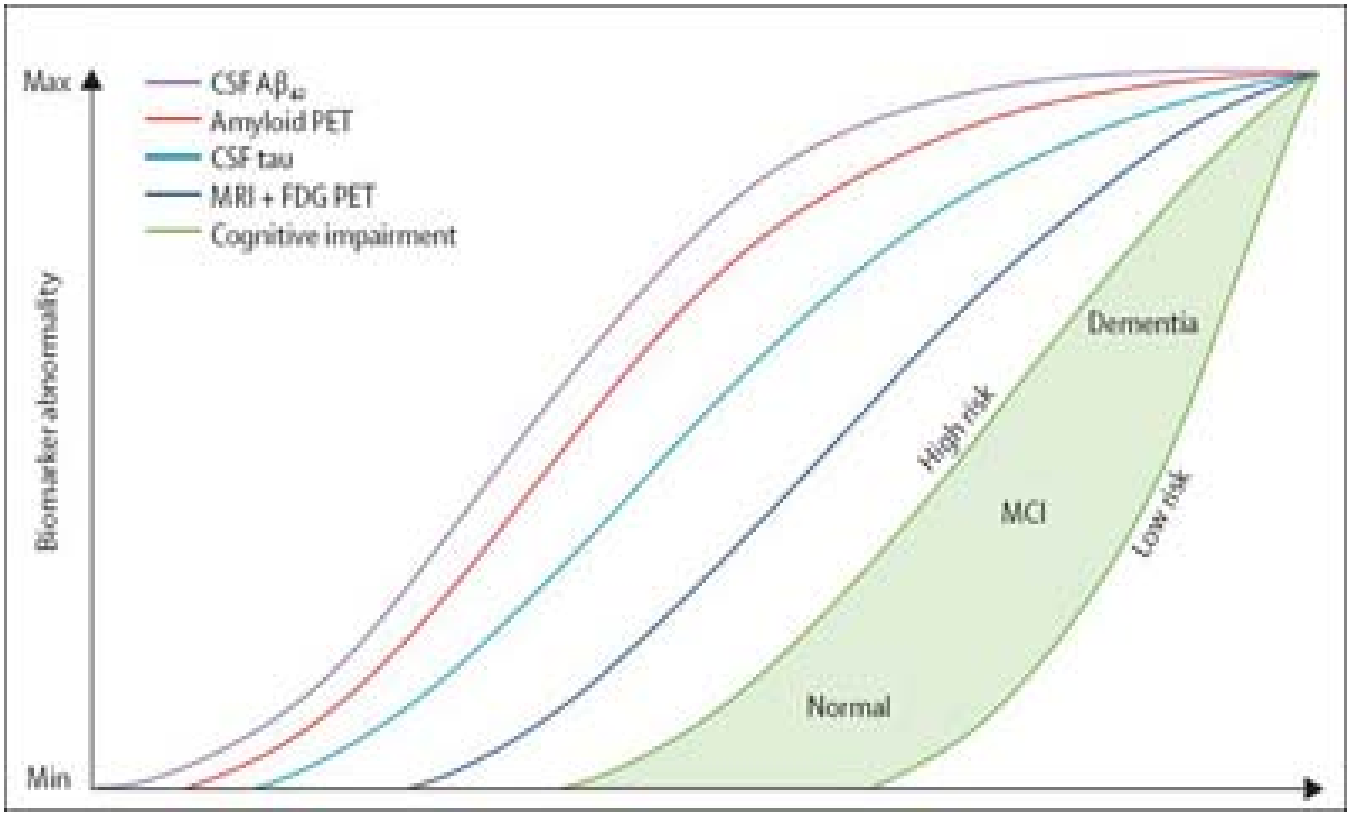
Identifies pathological process before clinical symptoms

Can be used for screening

Is proportionate to the severity of that process

Can be used as a marker for therapy

Cheap, acceptable



Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013 Feb;12(2):207-16

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

For the above definition, the following are not covered:

- Dementia secondary to alcohol or drug abuse / non-organic psychiatric illnesses

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.

Severe degree of impairment required in order to claim but some insurer offer an additional benefit upon diagnosis only.

Dementia – resulting in permanent symptoms

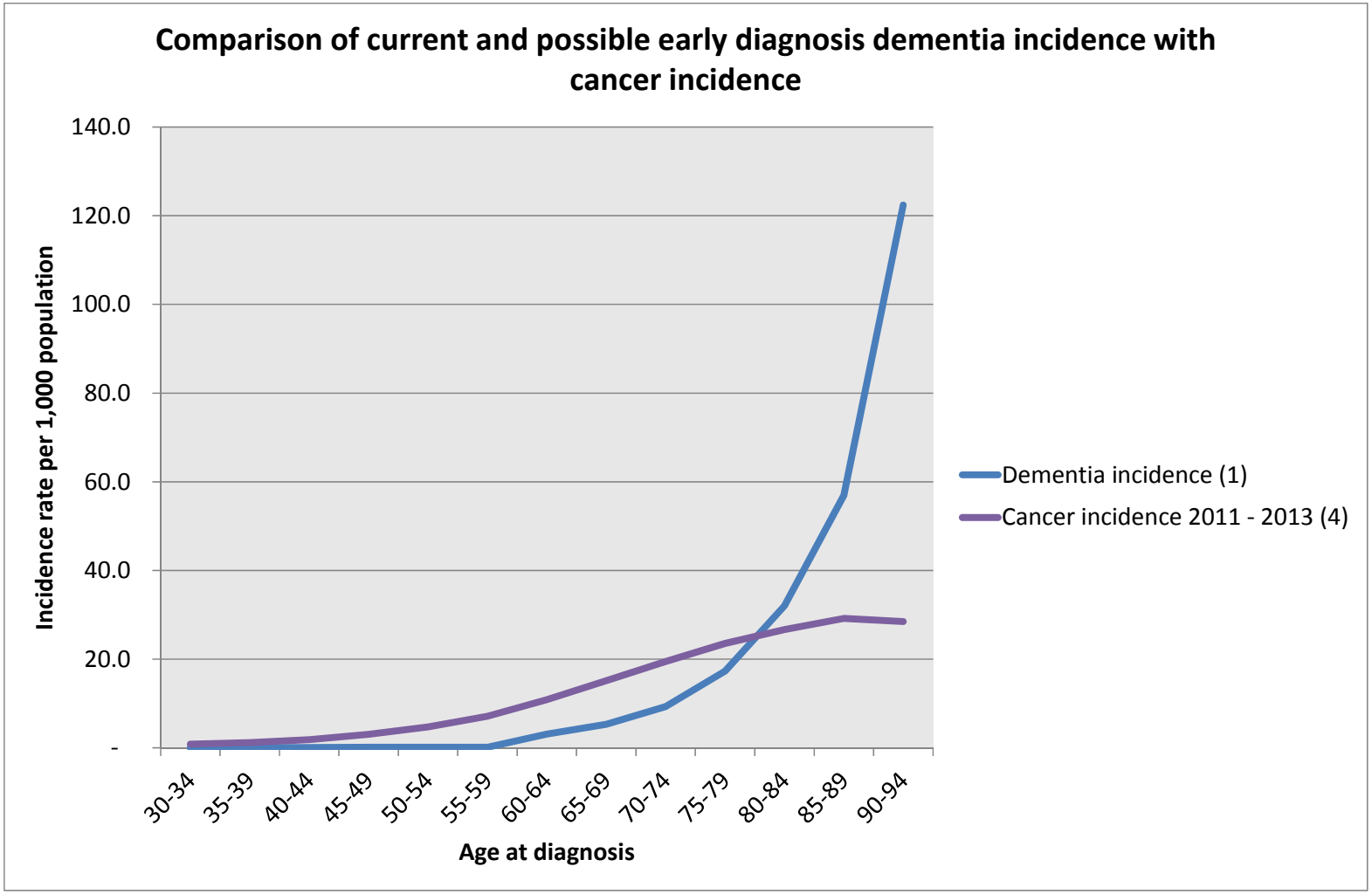
A definite diagnosis of dementia by a Consultant Neurologist, Psychiatrist or Geriatrician. There must be permanent clinical loss of the ability to do all of the following:

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

For the above definition, the following are not covered:

- Dementia secondary to alcohol or drug abuse / non-organic psychiatric illnesses

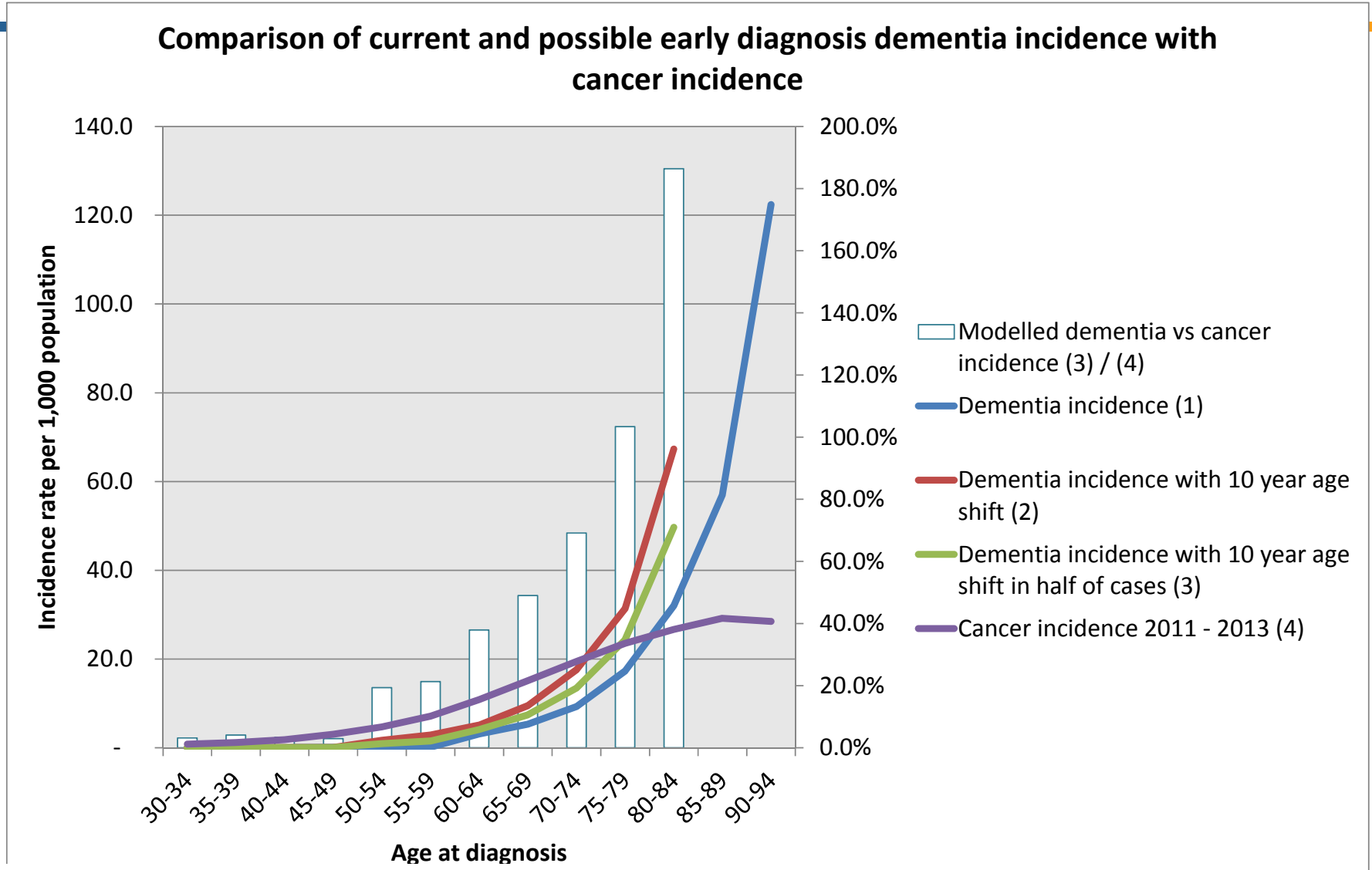
Effect of earlier diagnosis on dementia incidence



Sources:

- Cancer incidence (chart line 4): Cancer Research UK, http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence, Accessed April 2016 (average of male and female incidence)
- Dementia incidence (chart line (1) age 60+): Alzheimer's Disease International (ADI), London, World Alzheimer Report 2015: The Global Impact of Dementia, An analysis of prevalence, incidence, cost and trends, Chapter 3
- Dementia incidence (chart line (1) below age 60): Mercy L et al, Incidence of early-onset dementias in Cambridgeshire, United Kingdom, Neurology. 2008 Nov 4;71(19):1496-9

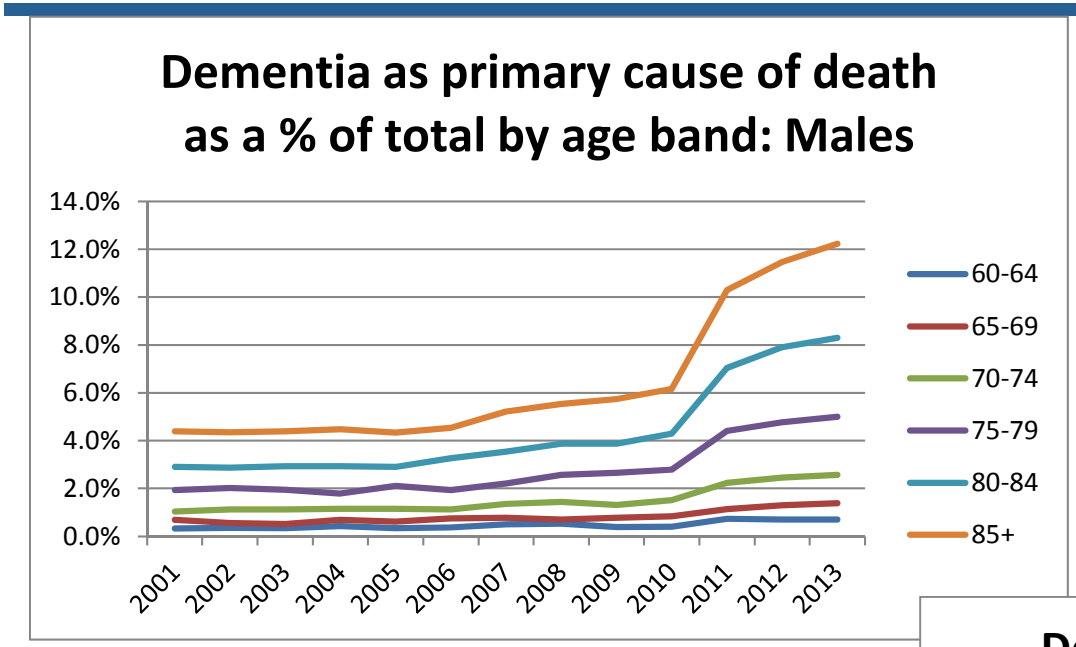
Effect of earlier diagnosis on dementia incidence



Sources are own calculations based on:

- Cancer incidence (chart line 4): Cancer Research UK, http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence, Accessed April 2016
- Dementia incidence (chart line (1) age 60+): Alzheimer's Disease International (ADI), London, World Alzheimer Report 2015: The Global Impact of Dementia, An analysis of prevalence, incidence, cost and trends, Chapter 3
- Dementia incidence (chart line (1) below age 60): Mercy L et al, Incidence of early-onset dementias in Cambridgeshire, United Kingdom, Neurology. 2008 Nov 4;71(19):1496-9

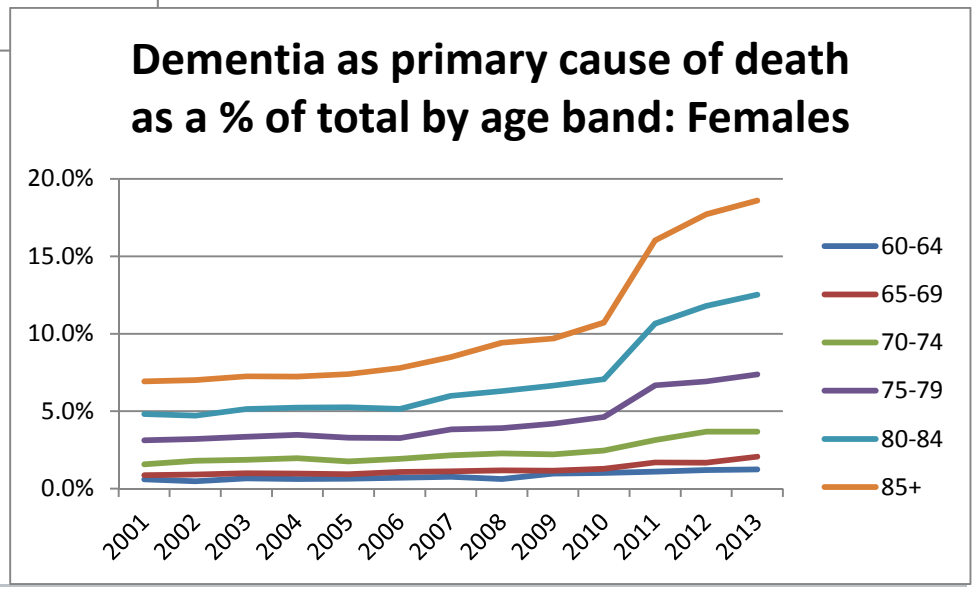
Mortality trends – Dementia deaths as a % of total



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

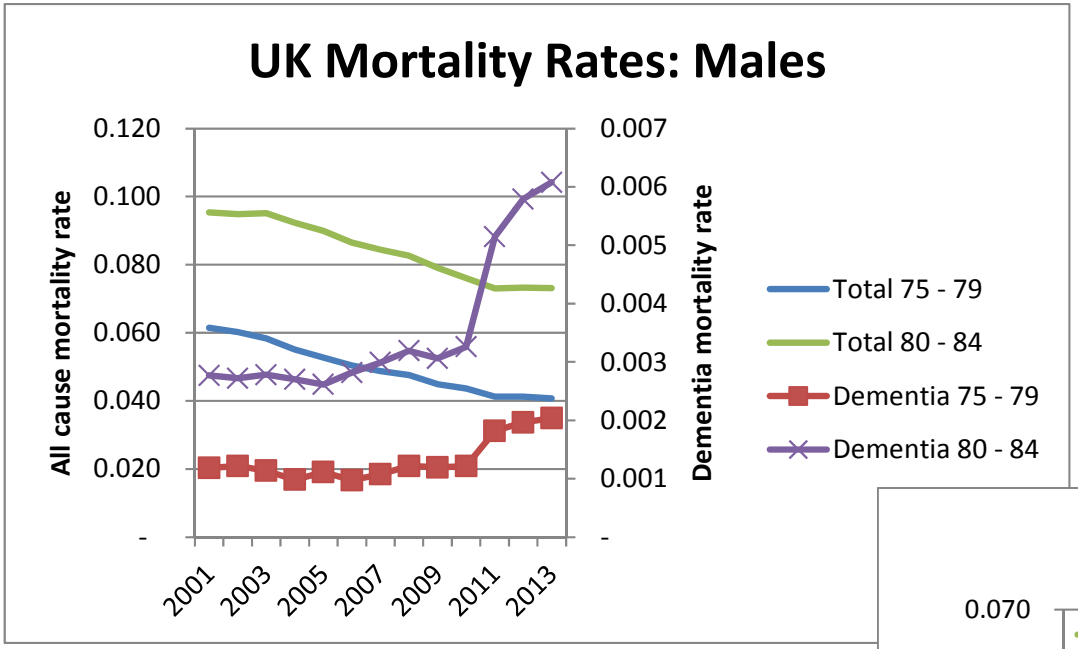
Vascular dementia was previously assigned to cerebrovascular disease.

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

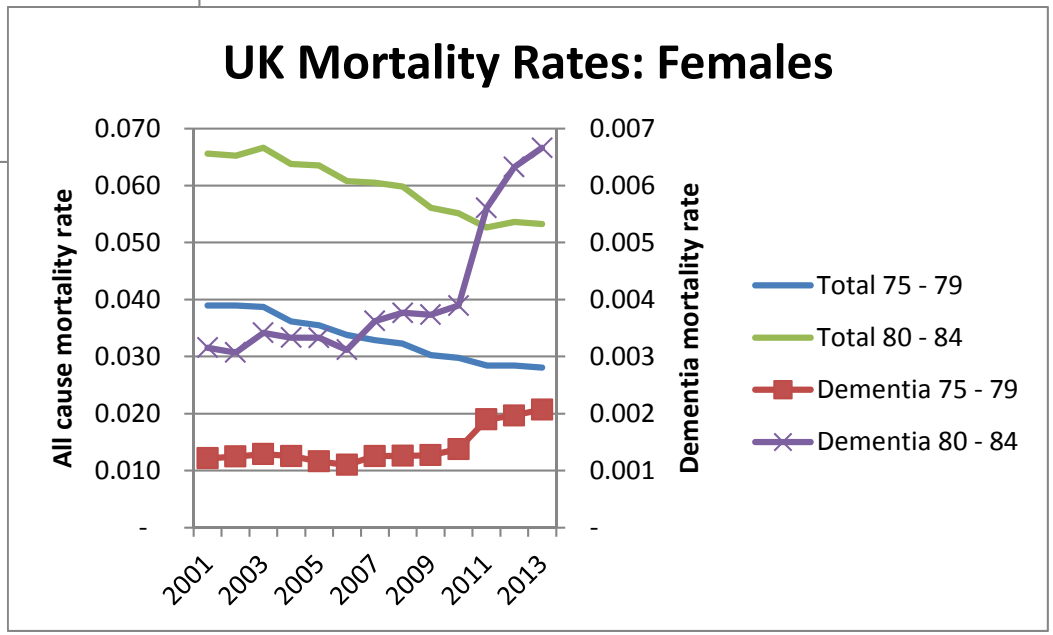


Source: ONS 21st Century Mortality dataset, England & Wales 2001–13

Mortality improvements by cause



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



Source: ONS 21st Century Mortality dataset, England & Wales 2001–13

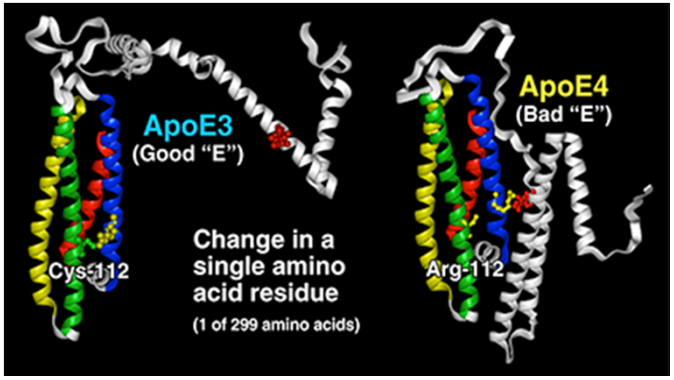
Alzheimer's Disease Genes: Insurance Case studies from the US

May 2016

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



http://gladstoneinstitutes.org/node/11431

- 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:
  - Slooter AJ et al. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. Arch Neurol. 1998;55:964–8.

- 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

Genetic testing and insurance purchasing decisions

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

- 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:

Ewbank D, Mortality Differences by APOE Genotype Estimated From Demographic Synthesis, Genetic Epidemiology 22:146–155 (2002)

https://www.rand.org/content/dam/rand/www/external/labor/aging/rsi/rsi_papers/2005_ewbank2.pdf

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

The material contained in this presentation has been prepared solely for informational purposes by Gen Re. The material is based on sources believed to be reliable and/or from proprietary data developed by Gen Re, but we do not represent as to its accuracy or its completeness. The content of this presentation is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

Disclaimer