Institute and Faculty of Actuaries

Evolving Embodiment of Risk:
The case of Alzheimer's Disease

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Roughly 850,000 now to double to 2050.
Projected increase in people with dementia in UK
Dementia UK London 2014

Economic impact of dementia

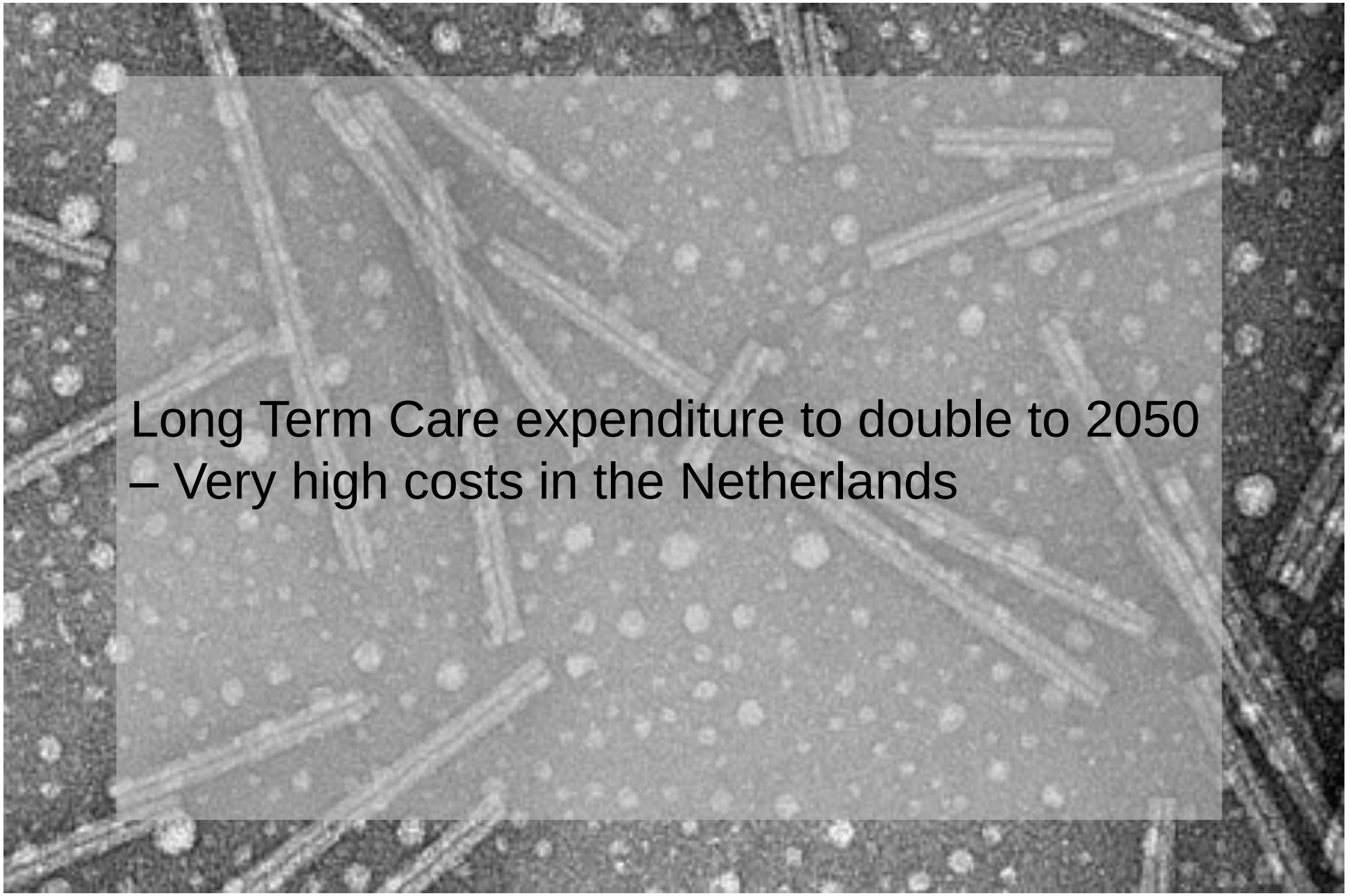
Overall impact £26.3 billion

£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)

Dementia UK 2014


Long Term Care expenditure to double to 2050
– Very high costs in the Netherlands

Rhetoric and Dementia

Critical update:

One disease. Millions of lives permanently disrupted.

The Alzheimer's Association, Alzheimer’s Disease 2015 Facts and Figures released today, highlights the devastating human and economic costs of the Alzheimer's epidemic. Alzheimer's Disease is taking more than memories — it's taking lives. (24/3/15)

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+ - 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

Cautions

Obesity & diabetes on the rise so will this be maintained?

China’s obesity prevalence has doubled in 30 years

Call to rebalance research less on diagnostics and treatment than on prevention

"Policies which address determinants of health in earlier life stages and enhance cognitive reserve for populations may have the greatest long term impact on reduction of dementia risk at given ages in later life as well as on population health more generally.“

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

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

Modifiable Risk Factors

Risk Factor	Relative Risk
Diabetes	1.39
Midlife hypertension	1.61
Midlife obesity	1.60
Depression	1.90
Physical inactivity	1.82
Smoking	1.59
Low education	1.59

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

Modifiable Risk Factors: Diabetes

	2013	2040
Diabetes cases prevented	23k	40k
Life years saved	92.7k	150k
State savings	321M	560M

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 vs Alzheimer's Disease

Dementia is syndrome

ICD-10 (WHO)
Memory decline. Particularly learning new information
Decline in at least one other domain of cognition such as judging and thinking, planning and organising etc.
To a degree that interferes with daily functioning
Some change in one or more aspects of social behaviour
There should be corroborative evidence that the decline has been present for at least 6 months

ICD 10 WHO 1993 Dementia

Dementia vs Alzheimer's Disease

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

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

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Not ‘just your age dear’

Prevalence Men

Increase to 20% at 90

Prevalence Women

Increases to 30% at 90

Dementia UK 2014

If not ‘just your age dear’…….

Assumptions

Not normal ageing

There is a period when the person is aware of mild problems

A period of cognitive impairment but not yet dementia

Mild Cognitive Impairment

Jessen et al (2010) Archives General Psychiatry 67. 414 et seq.

Mild Cognitive Impairment

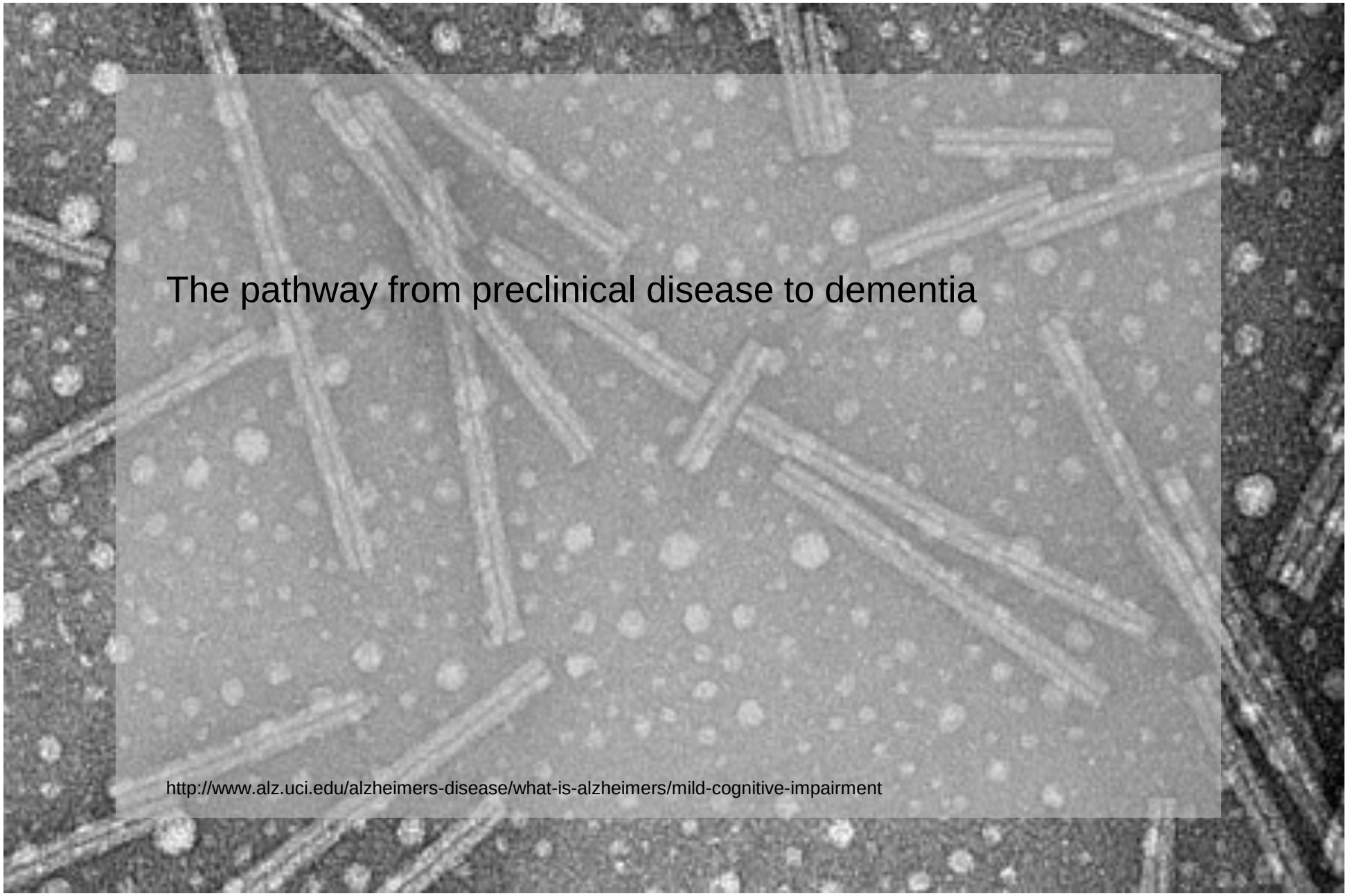
10 to 15% per year progress to dementia

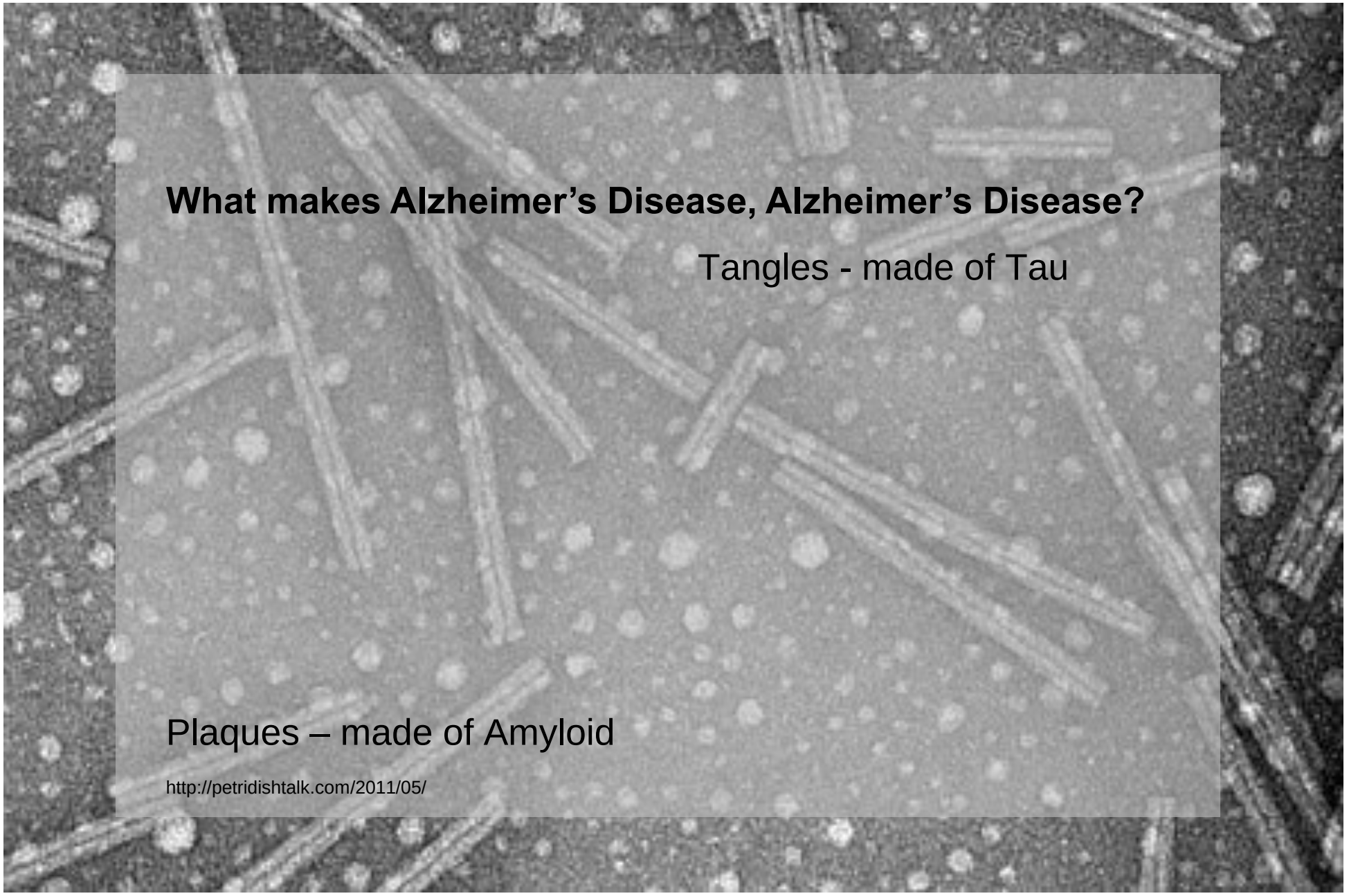
1 in 4 patients remain with MCI
Normal people 1 to 2 percent per year convert to dementia and 5 percent convert over five years

Over three years:-

- 1/3 improve
- 1/3 remain the same
- 1/3 develop dementia

(Bartlett & Burns 2014)


The pathway from preclinical disease to dementia
http://www.alz.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

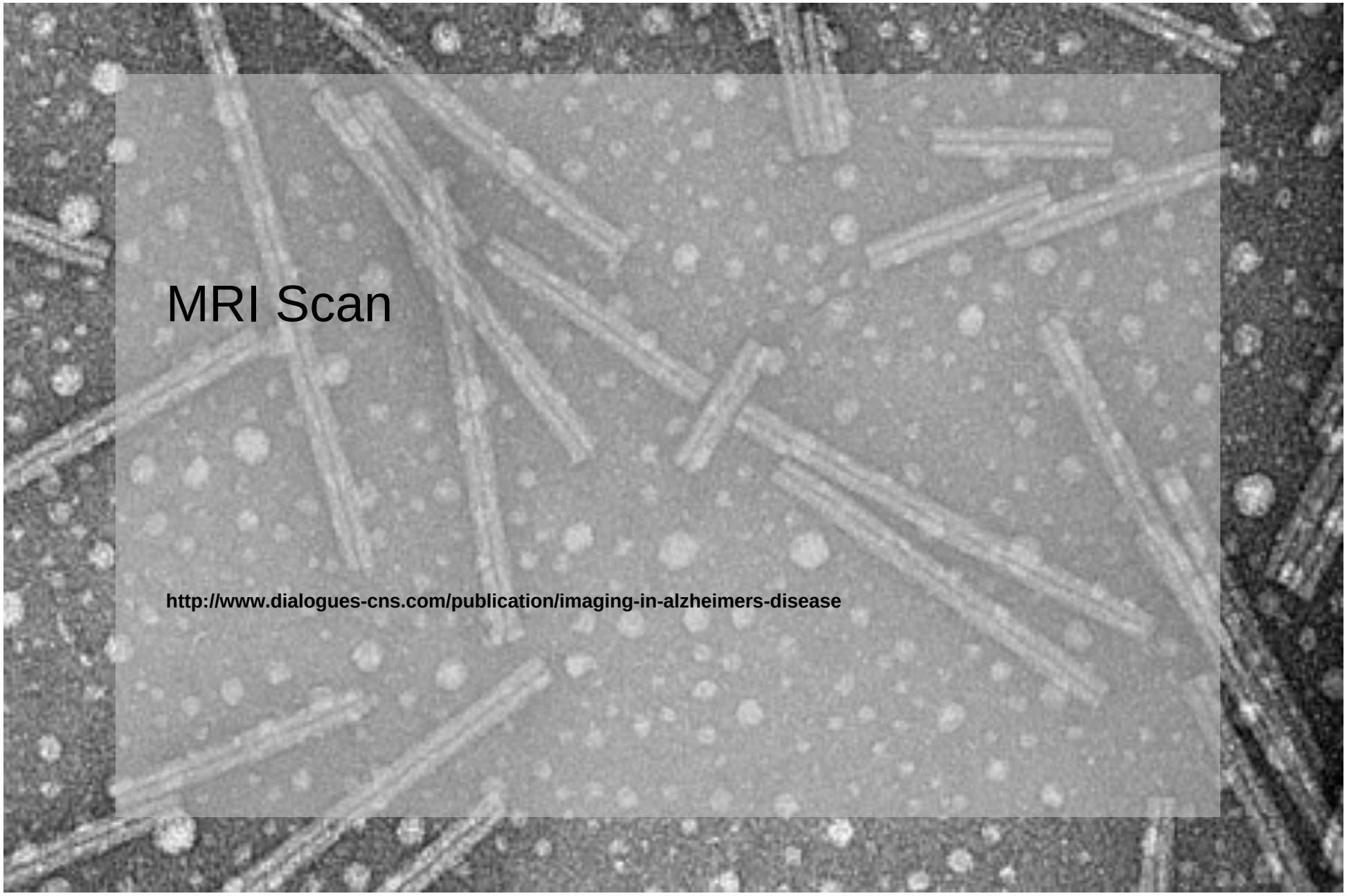
Biomarkers and embodying risk

‘(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.

CT scan

http://www.medscape.com/features/slideshow/alzheimers


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

FDG – PET scan

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

Amyloid PET

Amyloid PET scan

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

Poorer survival with low AB amyloid and raised 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 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

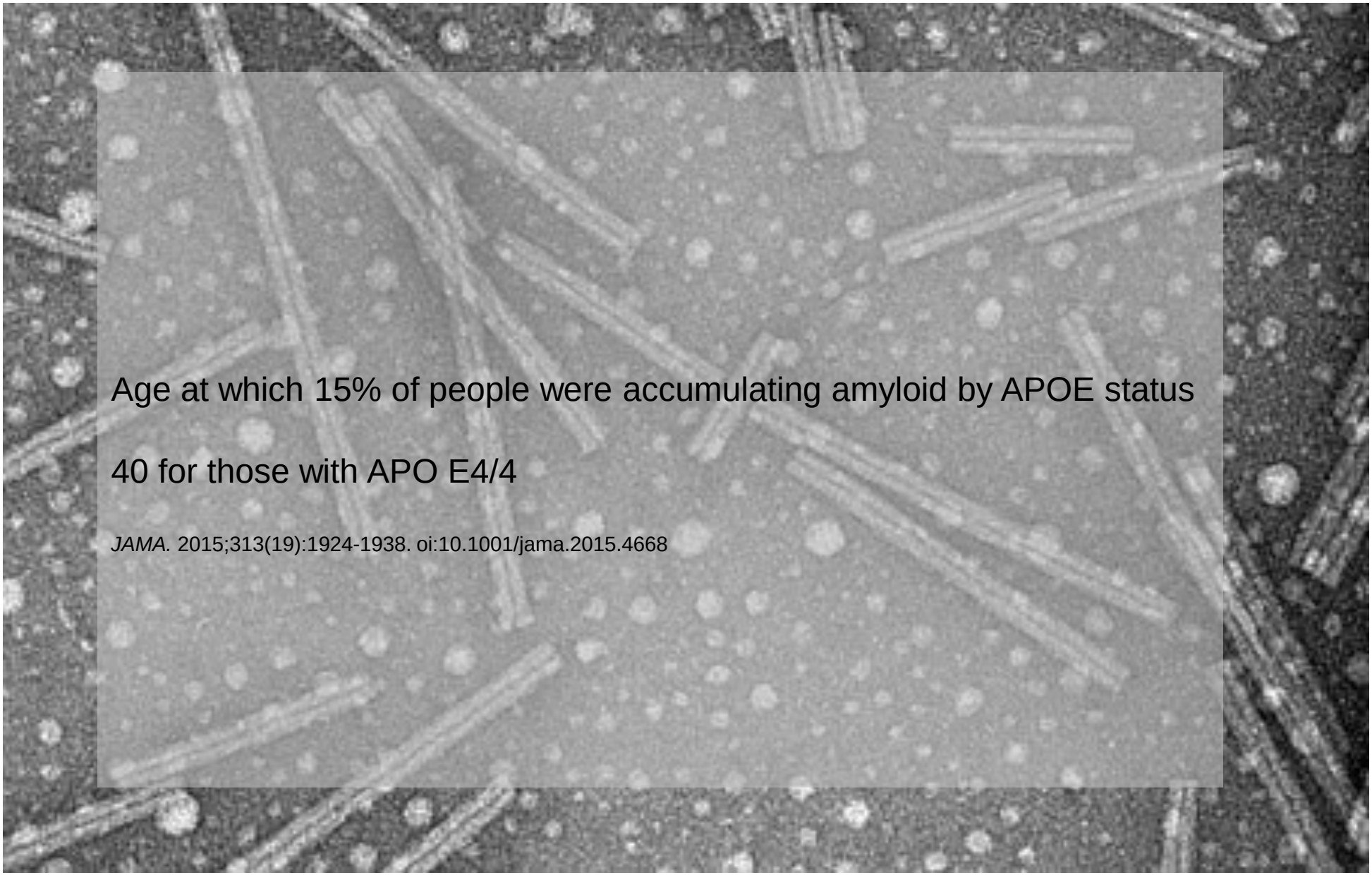
Not everyone with e4 develops the disease

Between 1/3 and ½ of those with LOAD do not have e4

Genetics: Late Onset Alzheimer's Disease

APO E 3 and 4
The effects of a single amino acid change

http://gladstoneinstitutes.org/node/11431



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

40 for those with APO E4/4

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


The cost of sequencing the entire human genome has decrease to just $60k

Genome Wide Association Studies

Strongest evidence for APOE involvement

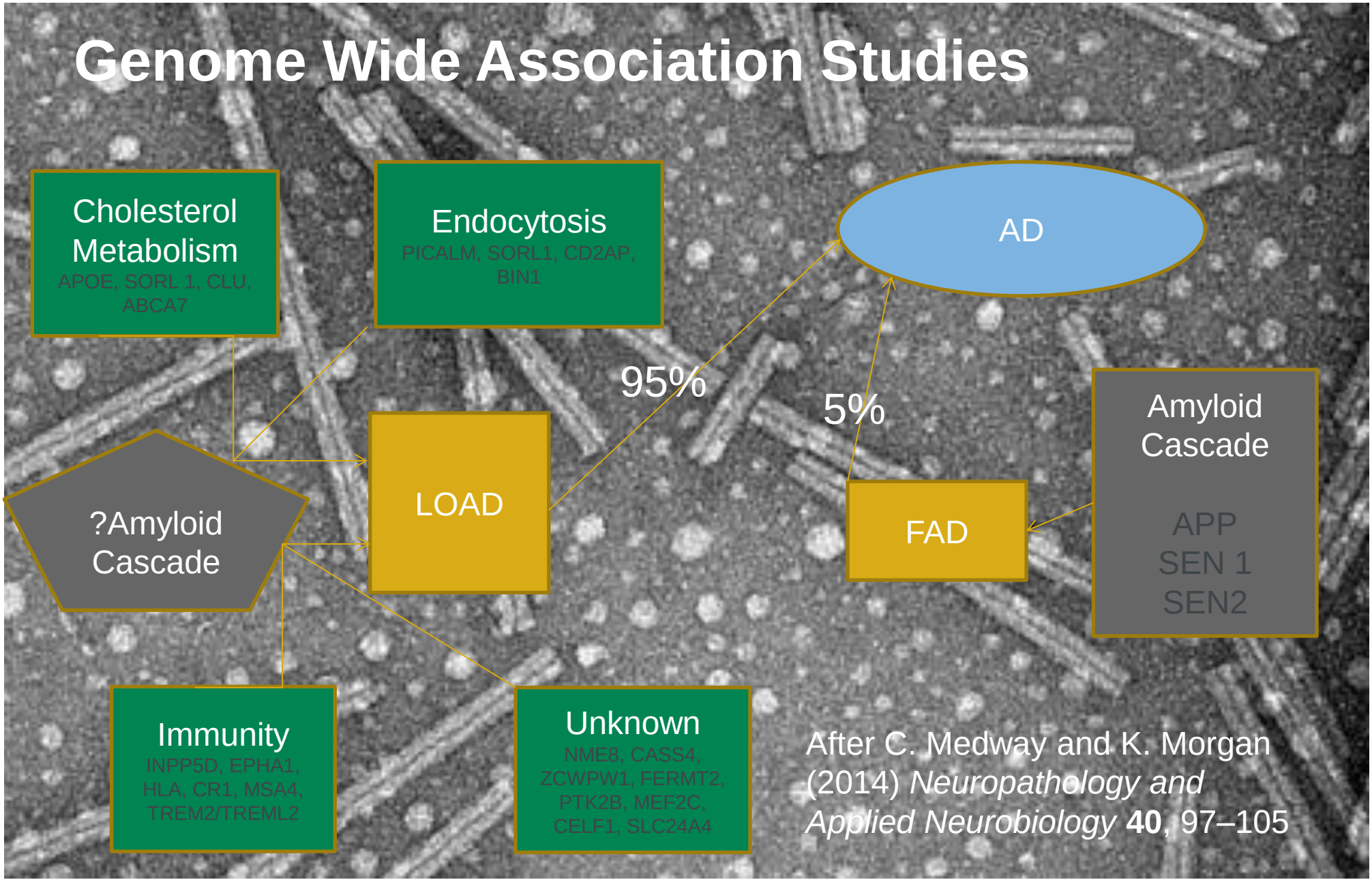
Complex interaction between multiple genes

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

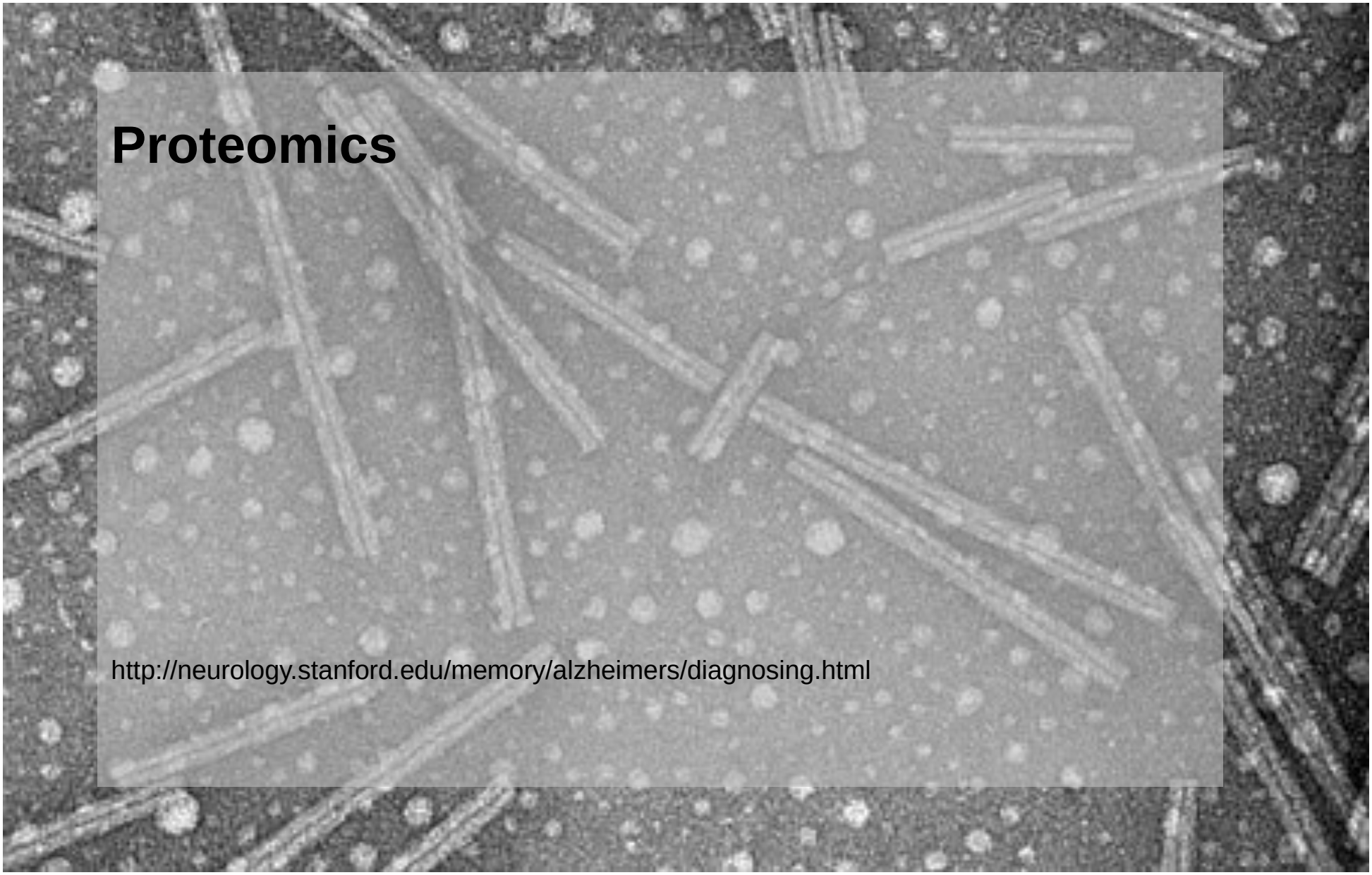
Easily accessible but not in contact with the brain

Blood is a complex fluid

Single molecule studies not useful

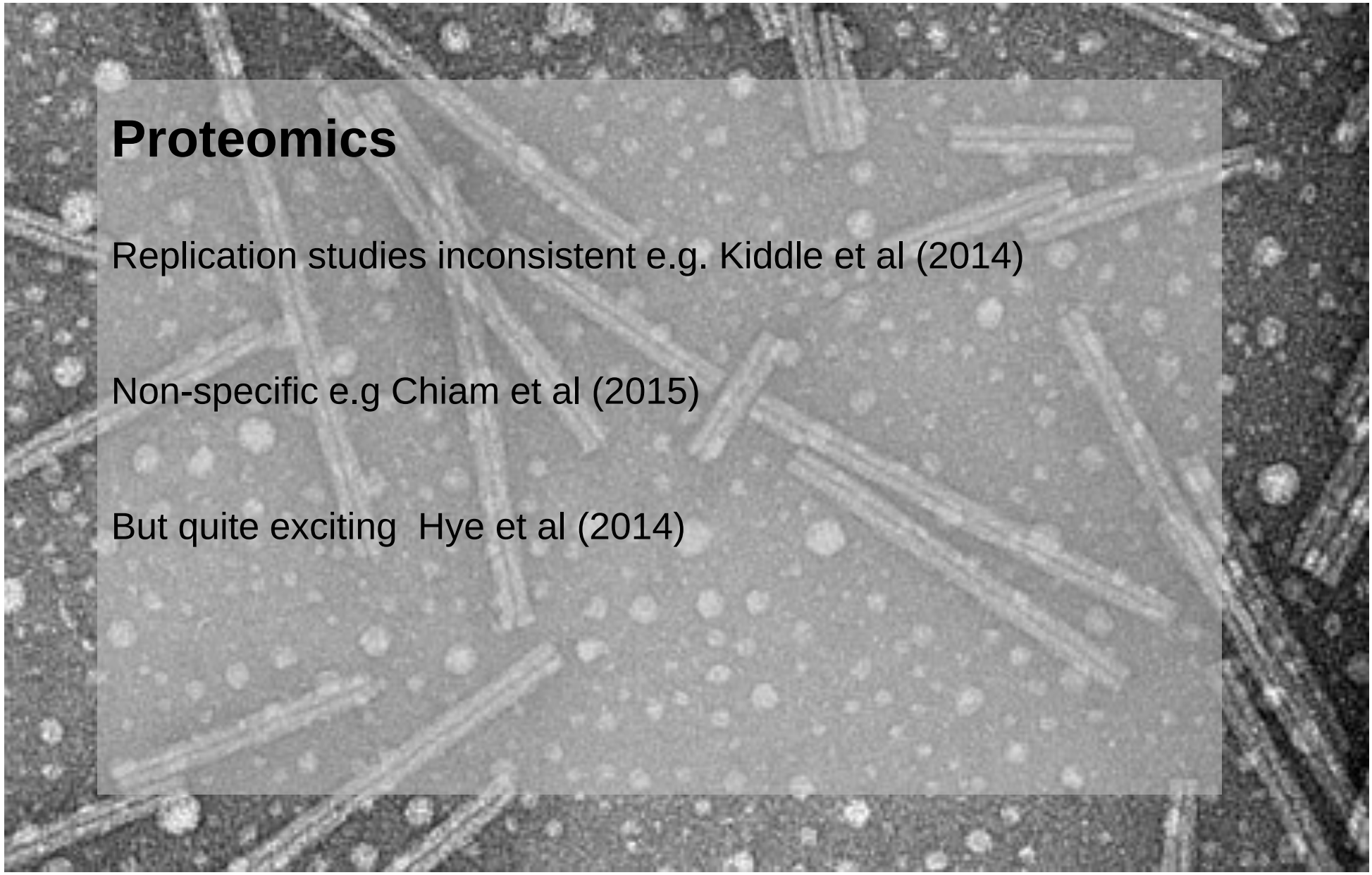
Proteomics – Identify a protein signature for a disease

Potentially a cheap and acceptable biomarker for presymptomatic AD



Proteomics

http://neurology.stanford.edu/memory/alzheimers/diagnosing.html



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

Relationship of biomarkers to the onset of cognitive problems

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

National Institute on Aging- Alzheimer's Association (NIA-AA) Classification 2011

Preclinical Stage

No cognitive impairment but biomarkers present

Mild Cognitive Impairment due to AD

Impairment on cognitive testing
Biomarker evidence
No impairment functioning

Dementia due to Alzheimer’s Disease

http://www.alzheimersanddementia.com/article/S1552-5260(11)00099-9/pdf

The *Risk Evaluation and Education for Alzheimer's Disease* (REVEAL)

Educational session about AD

APOE testing

Informed of results and three further sessions over 12 months

At one year – 27% remembered accurately

50% had the broad gist correct

23% nothing or incorrectly

Lock, M. (2013) The Alzheimer Conundrum

Increasing Complexity

Complex susceptibility genes identified

Modified by epigenetic factors

How do doctors manage these issues?

Effects
….. ”can initiate or inhibit action, and increase or reduce, or transform anxiety about genetic embodiment”

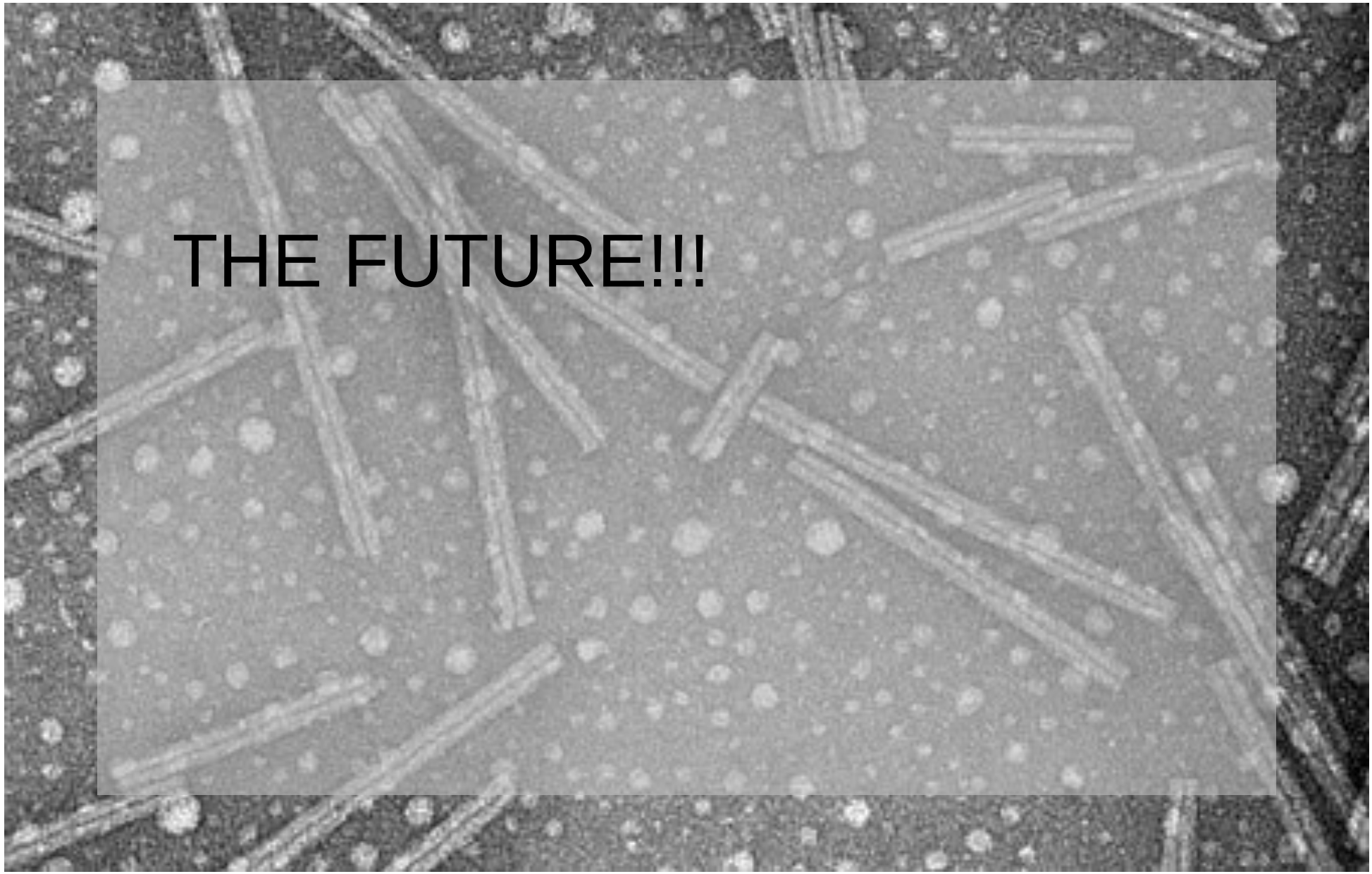
Lock, M. (2013) The Alzheimer Conundrum

‘I know what you told me but this is what I think’

Communicated risk not taken at face value even in those who recalled risk correctly at six weeks
69.3% higher, 30.7% lower
‘Anchoring and adjustment bias’
Linnenbringer et al (2010) Genet Med. 12. 219 –227

Kinscapes, Timescapes and Genescapes
http://orca.cf.ac.uk/39555/1/Kinscapes,Timescapes,and%20genescapes.pdf

Remain major problems in imparting and understanding probabilistic information about susceptibility
Information eclipsed by lay understanding


THE FUTURE!!!

Challenges

‘(Genetic) technologies permit us to speculate with much greater precision than was formerly the case about who may be struck by misfortune…’ Lock (2013)

Life insurance
Critical Illness
Retirement annuities
Long term care

Vehicle insurance
Public liability
Employers liability

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