FOCUS
Forum Of Claims and Underwriting Scotland

FOCUS……..
ON Dementia

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SCOR
The Art & Science of Risk | Life

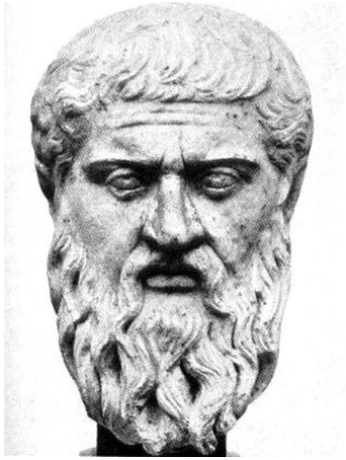
- What is dementia? – etymology and definition
- What causes dementia?
- Dementia syndromes and pathologies
- How is dementia diagnosed?
- Underwriting considerations
- Treatment

Dementia

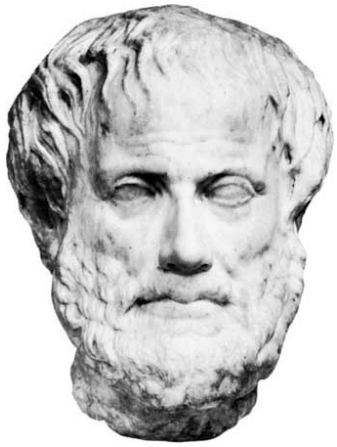
"A ***chronic*** *or* ***persistent*** disorder of mental processes caused by brain **disease** or **injury** and marked by memory disorders, personality changes and impaired reasoning"

- Dementia is a *clinical diagnosis*
- Alzheimer's disease is commonest cause but dementia is **NOT SYNONYMOUS** with Alzheimer's disease, which is a *pathology* . Usually cannot be diagnosed unequivocally during life – **NB underwriters**!!
- Dementia comprises several *clinical syndromes* reflecting anatomical sites of pathological predilection (*eg hippocampus, parieto-occipital regions in Alzheimer's disease, frontal and temporal lobes in FTD eg due to Pick's disease*)
- Dementia can be the consequence of a very large number of *different diseases and pathologies*. One pathology may predominate but pathology is often **mixed** (*eg Alzheimer's plus vascular disease*)

Pythagoras
570 – 495 BC



Plato
?428- 348 BC



Aristotle
384 – 322 BC

Cicero
106 – 43 BC

DEMENTIA

Latin – '*demens*' = 'mad' or 'out of one's mind'
Chinese – 'foolish old person' 癡呆.
OED Synonyms: mental illness, madness, insanity, derangement, lunacy

Pythagoras – dementia is a condition of the '**senium**' (*mental and physical decay due to old age and advanced age, 63 yrs plus*)

Plato and later **Aristotle** taught that dementia was an inevitable consequence of aging. Elderly unsuited for any position of responsibility

*For hundreds of years, '***senile dementia***' or* **'senility'** considered a normal part of life

But the Roman, **Cicero** said that it only affected '*those men who were weak willed*' – i.e. not necessarily a natural consequence of aging.

Alois Alzheimer

‘Pre-senile’dementia

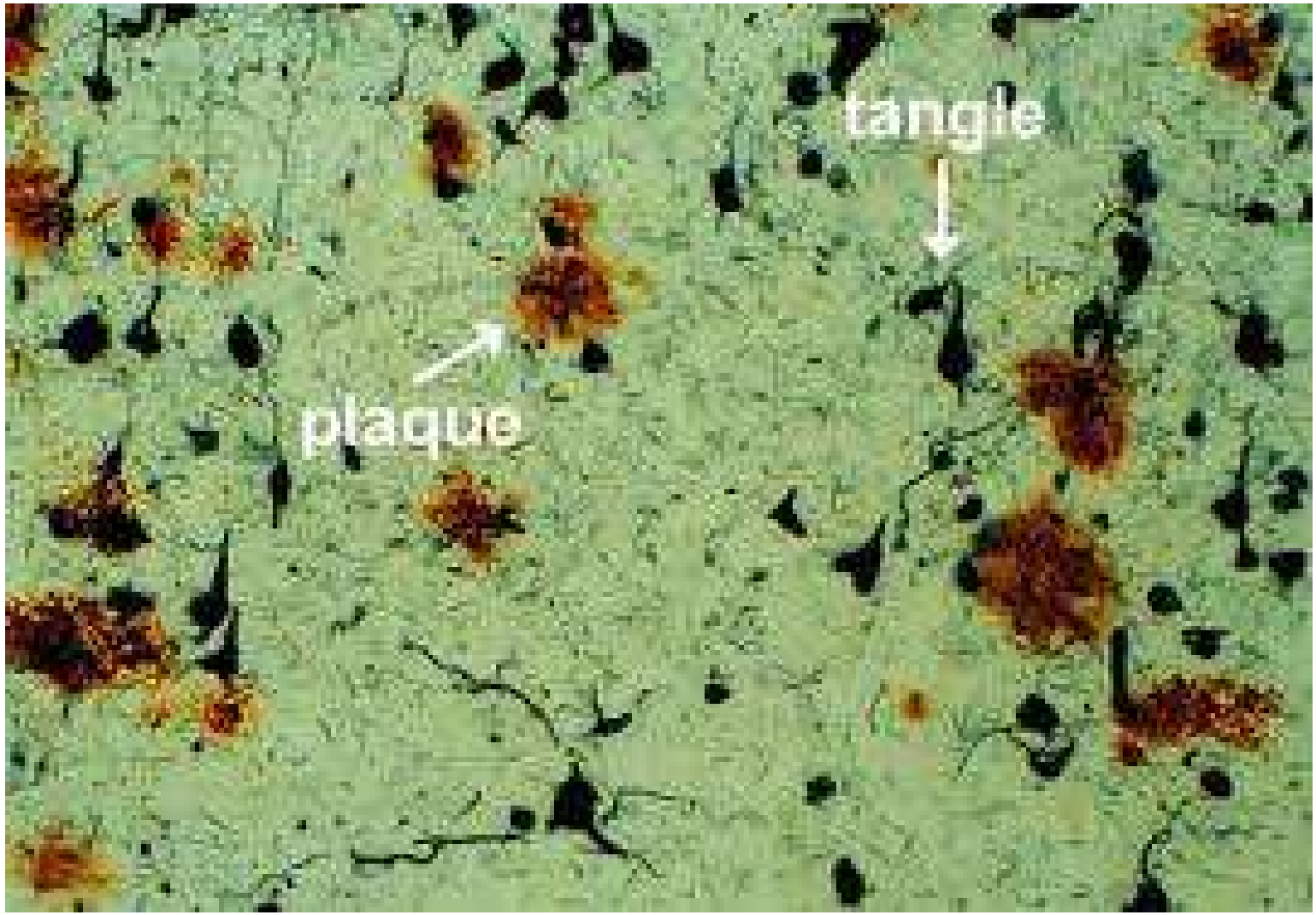
Until end of C19th ‘dementia’ = any form of mental derangement in which *individuals lost capacity to reason*

Included ‘mental illnesses’ in **younger people** e.g. *dementia praecox* of schizophrenia and potentially reversible or treatable diseases e.g. *syphilitic dementia* (a consequence of spirochaetal infection). Virtually eradicated by penicillin

Dementia in under 65s termed ‘pre-senile’ dementia

1907 – Alzheimer reported pathology in brain of a 51 year old German woman with dementia. Described interneuronal amyloid plaques and intraneuronal neurofibrillary tangles

Described as *Alzheimer’s disease*, “a rare form of pre-senile dementia”, by Kraepelin in 1910



Alzheimer's disease – amyloid plaques and neurofibrillary tangles

Amyloid plaques =
β-pleated sheets of APP

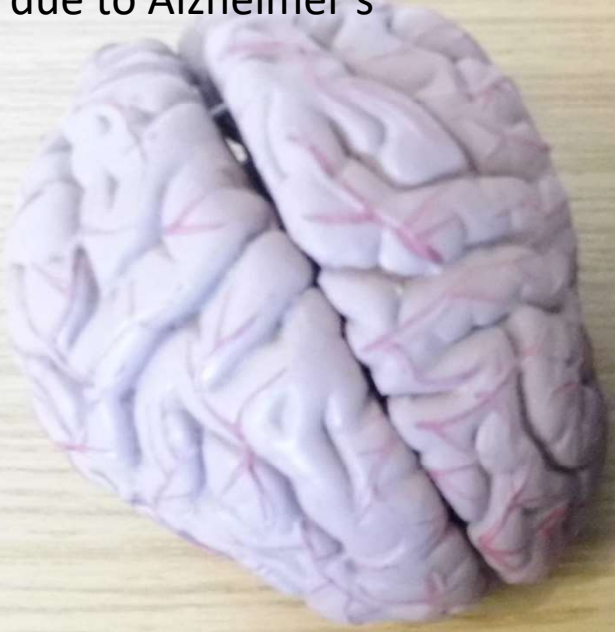
Tau protein
aggregates

Dementia and Aging in early C20th

- **1920** – Dementia denotes '*permanent, irreversible mental deterioration'*
  - Pre-senile dementia (<65 yrs) e.g. Alzheimer's *uncommon*
  - 'Senile dementia' uncommon until after WWII due to early age of death
- **Post WWII** over 65s in industrialised countries increased from 5% in 1945 to 15-20% of population by C21st
  - Increase in prevalence of dementia linked to aging
  - Major advances in understanding of cerebrovascular diseases
  - Belief that senile dementia was due to *cerebral arteriosclerosis* (?blockage of major arteries ?small vessel disease with multiple small strokes)
- **Cerebrovascular disease believed to be the main cause of 'senile dementia' during the first half of C20th**
- **1960**s onwards: increasing evidence of link between neurodegenerative disease (e.g. Alzheimer's and other forms) and cognitive decline

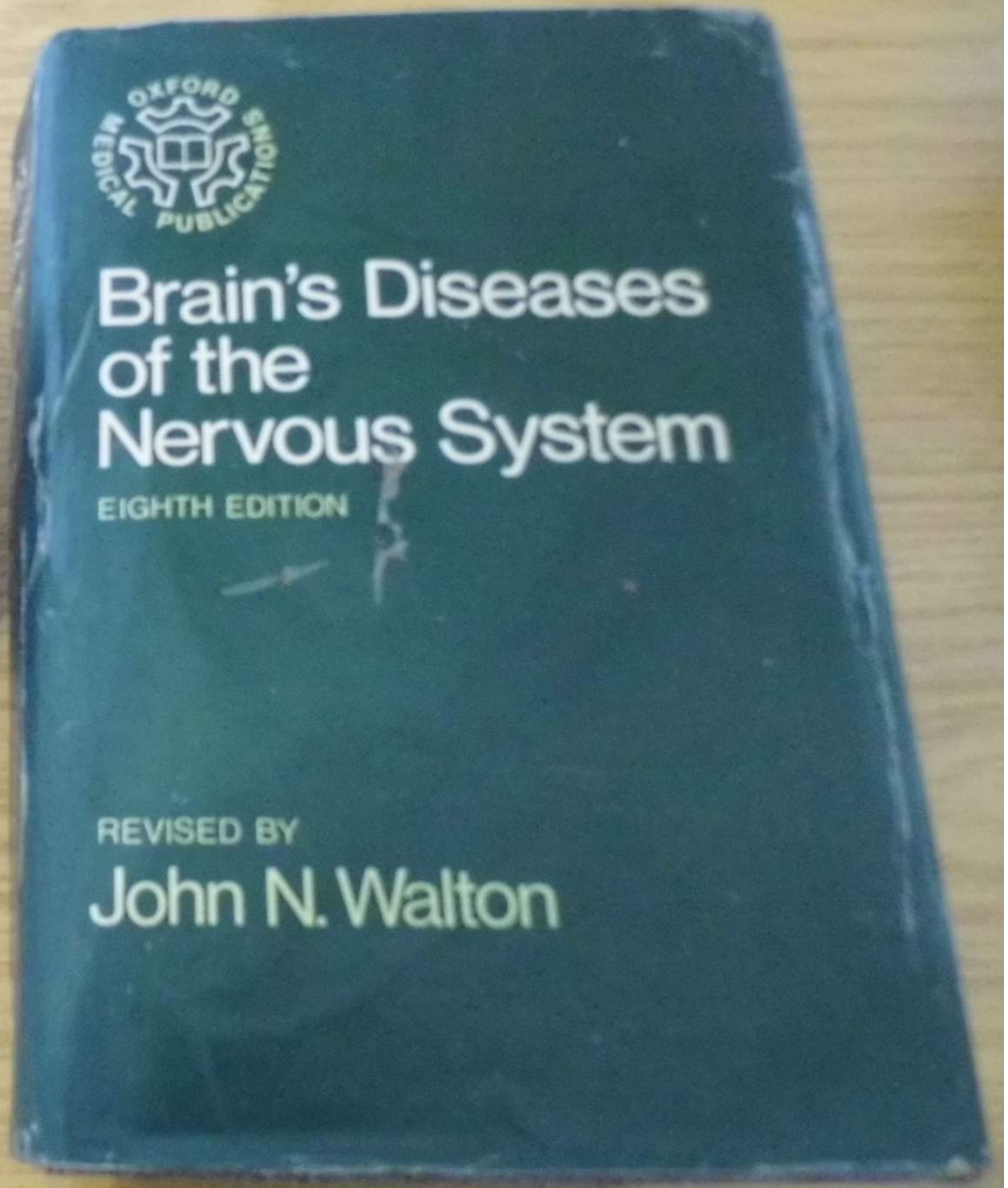
1976 Robert Katzman

- Most senile dementia is *pathologically identical* to pre-senile dementia due to Alzheimer's disease



"These changes are characteristic of senile degeneration of the cortex"

"There seems no doubt that Alzheimer's disease is essentially a premature senile change"



What causes dementia?

Classification

In 2017 dementia classification changed by ICD and WHO from a 'Mental and Behavioural Disorder' to 'Disease of the Nervous System'.

*A **CONSEQUENCE** of certain brain diseases*

- ***Primary** - cognitive and behavioural abnormalities paramount*
  - *Alzheimer's 50 -70% Lewy body dementia 20% frontotemporal dementia (FTD) 15%*
  - *Vascular dementia 15 - 25%. Often co-exists with other dementia pathologies*
- ***Secondary** – dementia may occur as part of another disease. Many causes!!*

  Neurodegenerative – PD, MSA,PSP, CBD

  Structural – NPH, chronic subdurals, benign tumours

  Infections – TB, syphilis, HIV

  Trauma – Chronic traumatic encephalopathy

  Immunological – MS, lupus

  Metabolic and endocrine – hypothyroidism, B12 deficiency

  Drugs and toxins – alcohol, cannabis

  Pathophysiologies – Chronic epilepsy

  Other – Prion diseases eg CJD
- ***Mixed** pathology dementia common eg Alzheimer's + vascular dementia*

Dementia syndromes and pathologies

Principles

- A *syndrome* is a collection of stereotyped symptoms and signs that identifies a particular *clinical entity* but not necessarily a specific disease eg *parkinsonism* (a syndrome that can be seen in many diseases) v *Parkinson's disease* (a disease associated with a specific pathology)

- Different dementia syndromes reflect the predilection of particular brain pathologies to affect different brain areas, at least initially

- The clinical manifestations are the consequence of the **anatomy** of the principal causative brain pathology, not the pathology *per se*

- *Microscopically, the neurodegenerative primary dementias are characterised by aggregations of aberrant proteins that lead to neuronal death and brain atrophy. But we don't know why this happens.*

Alzheimer's Disease (AD)

50 – 70% of dementia cases

EARLY

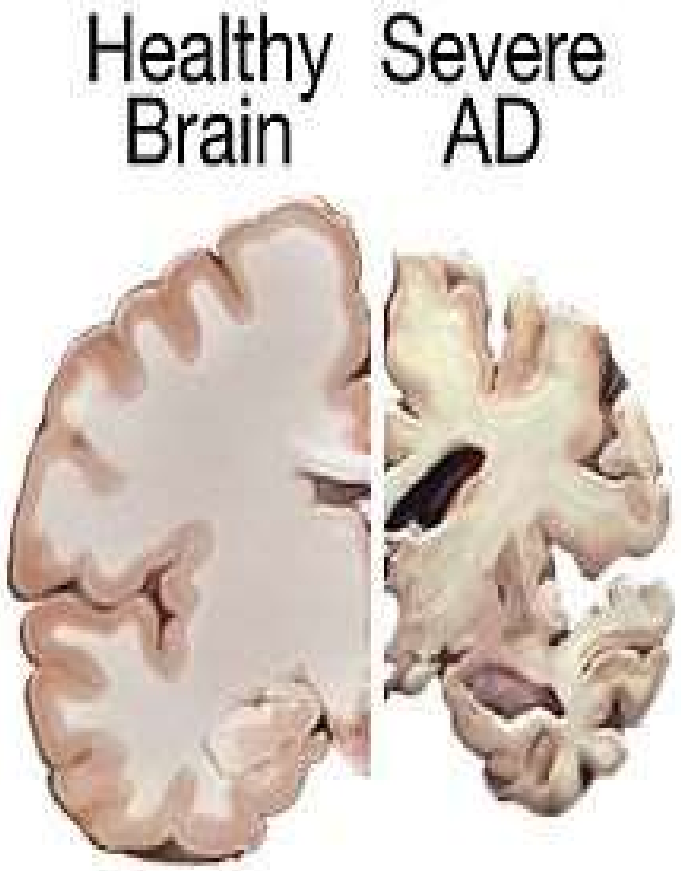
Hippocampus, temporal lobes – short term memory loss, word finding difficulites. Later, aphasias

Parieto-occipital cortex – visuo-spatial disorder. Getting lost, inability to tell time, draw clock face etc

LATER

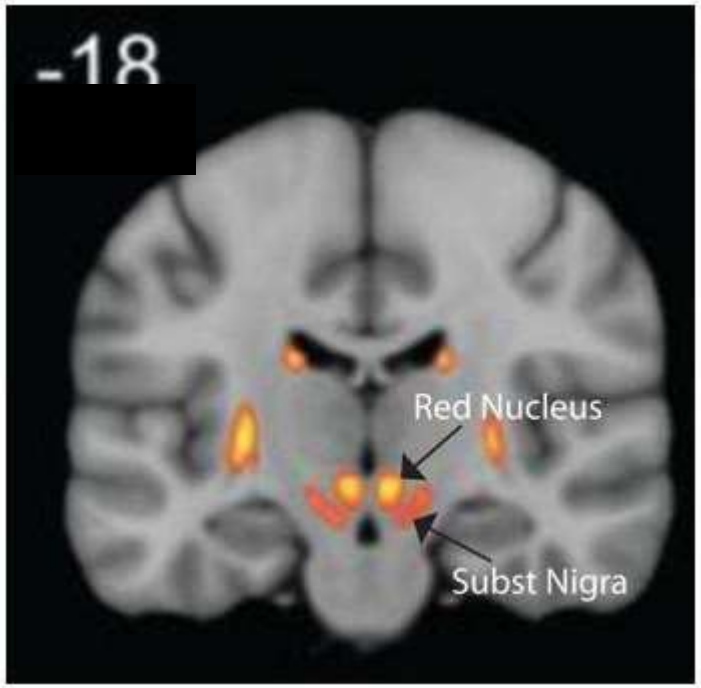
Frontal cortex – Impaired reasoning, judgement, insight, decision making

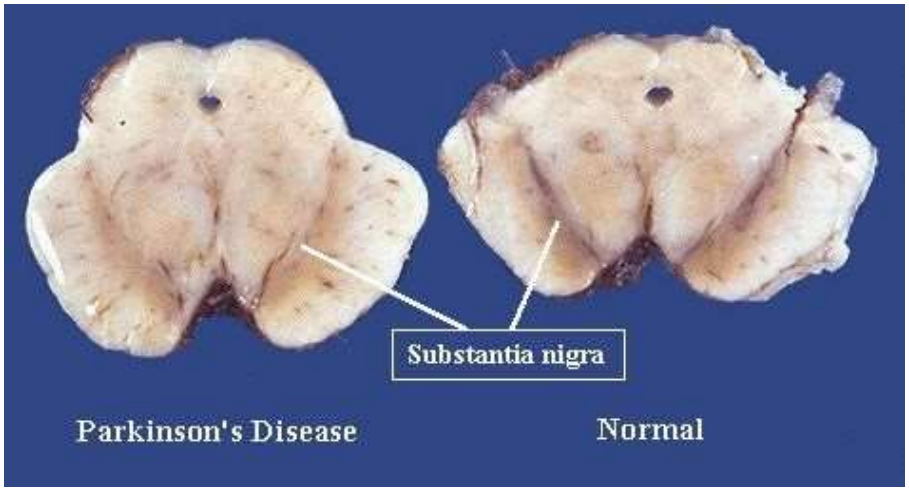
Global - Personality breakdown, failure of control of vegetative functions

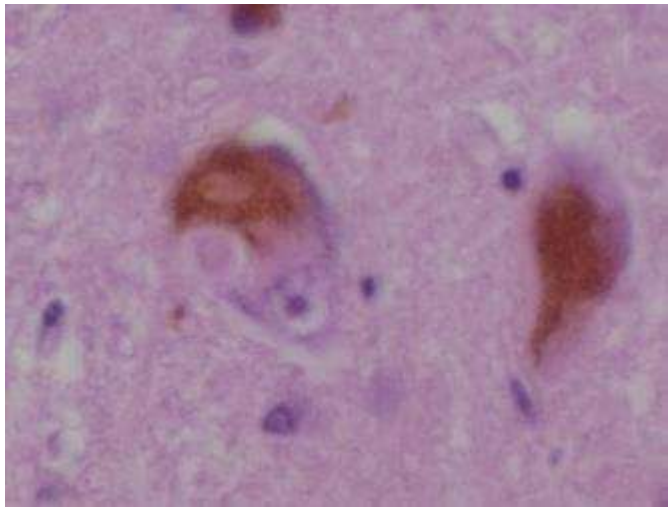


Lewy body associated dementia

10% of cases







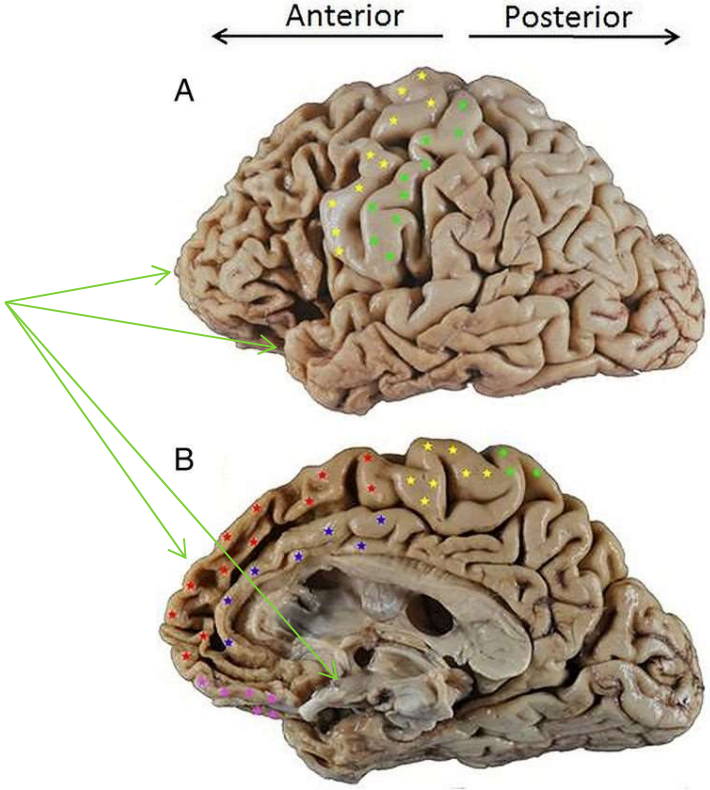
Lewy bodies (*α-synuclein aggregates*)

PD with cortical Lewy bodies
Cortical Lewy body disease } **± AD/vascular**

- **Parkinsonism + 'subcortical' dementia**
  - Apathy, withdrawal, slowness of thought and action.
  - REM sleep behaviour disorder
  - Visual hallucinations in clear consciousness (animals, people, shadows
  - Other cortical dementia symptoms

Frontotemporal dementia (FTD)
15% of cases

- Frontal and temporal lobar atrophy



Pathologies

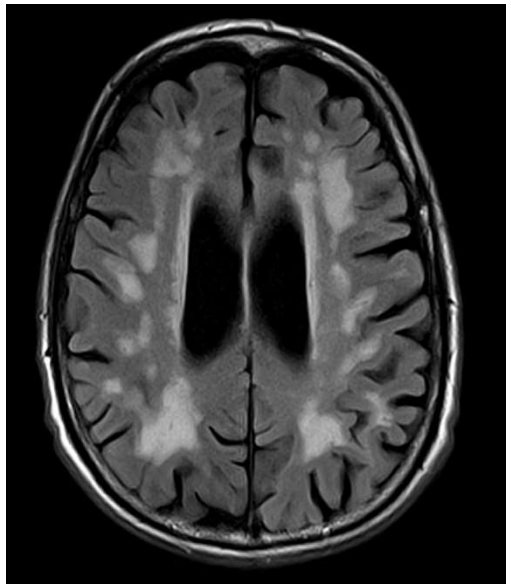
- Tauopathy – Pick's disease
- TDP43 (link to MND)
- FUS – sarcoma protein

Clinical syndromes

- *Frontal lobe syndrome*
  - Behavioural/personality
- *Temporal lobe syndromes*
  - Semantic dementia
  - Progressive non-fluent aphasia

Vascular dementia
15 – 25% of cases

- Second commonest cause of dementia
- Linked to hypertension, diabetes, hyperlipidaemia, smoking – ***preventable***
- May be involved in Alzheimer pathogenesis, common in 'mixed dementia'
- Very many forms but most common are:
    - Multi-infarct dementia – cortical or subcortical (lacunar)
    - Small vessel disease
    - 'Strategic infarct'
- Recently grouped as 'Vascular Cognitive Disorder'
- Two main presentations:
    - Slowly progressive global cognitive impairment
    - Step-wise deterioration caused by successive strokes
- Diagnosed by imaging eg MRI



How is dementia diagnosed?

- Dementia is largely a condition of the elderly
- Cognitive decline is a feature of normal aging (senility). Many other co-morbidities
- Dementia is a consequence of brain *disease*, not aging

Where does 'senility ' end and 'dementia 'begin?

'Dementia' requires three conditions to be fulfilled:

- Objective evidence of cognitive decline below limits defined for the age matched population as defined by cognitive function tests
- Chronic and progressive decline
- Interferes with normal function

- *Diagnosis*
  - Neurological examination
  - Cognitive function test(s). Tests for depression (pseudo-dementia)
  - Blood tests (mainly to exclude treatable conditions)
  - Neuroimaging
  - Sometimes ancillary investigations: radionuclide scanning (SPECT, FDG-PET, DaT, BiP etc), blood and CSF biomarkers
- *Diagnostic conundrum*
    - **Does patient fulfil diagnostic criteria for dementia?**
    - **What is the phenotype/syndrome?**
    - **What is the likely *principal* pathology**

Diagnostic pathway - I

- ***History***
  - From patient and in particular *a relative or 'significant other'.* Whose problem??
  - *Education, work history* – pre-morbid state
  - *Previous and Family history* – most dementia diseases have a genetic component. Head injury? Vascular disease?
  - *Drugs and alcohol*
- ***Examination***
  - *Typically normal in AD. ?Impaired smell/taste.Behavioural clues*
    - *Memory. 'Consultation sign' in AD*
    - *Vascular risk factors, episodic deterioration in VaD*
    - *REM sleep disorder, hallucinations in clear consciousness in DLB*
    - *Tactless remarks, loss of empathy and insight, sexual disinhibition, aggression in FTD*
  - *Focal signs in lobar atrophy, VaD eg. gait praxia*
  - *Parkinsonism in DLB*
    - *Supranuclear gaze paresis in PSP*
    - *Cortical sensory loss in CBD*
    - *Chorea in HD*
  - *Frontal release signs in FTD*

Cognitive Function Tests

- Many cognitive functions tests available but no single test can detect or diagnose all different forms of dementia
- All are biased to AD, many lack sensitivity to mild disease
- All these tests examine cognitive function in several functional/anatomical domains:

  Temporal lobes and connections
  - Orientation in time and space
  - Attention
  - Memory
  - Language
- *Parieto-occipita*l: visuospatial functions
- *Frontal*: apraxias, executive functions

MMSE classification	
≥24	Normal cognition (?)
19 – 23	Mild Cognitive Impairment (MCI)
10 – 18	Moderate dementia
≤9	Severe dementia

Short Cognitive Tests

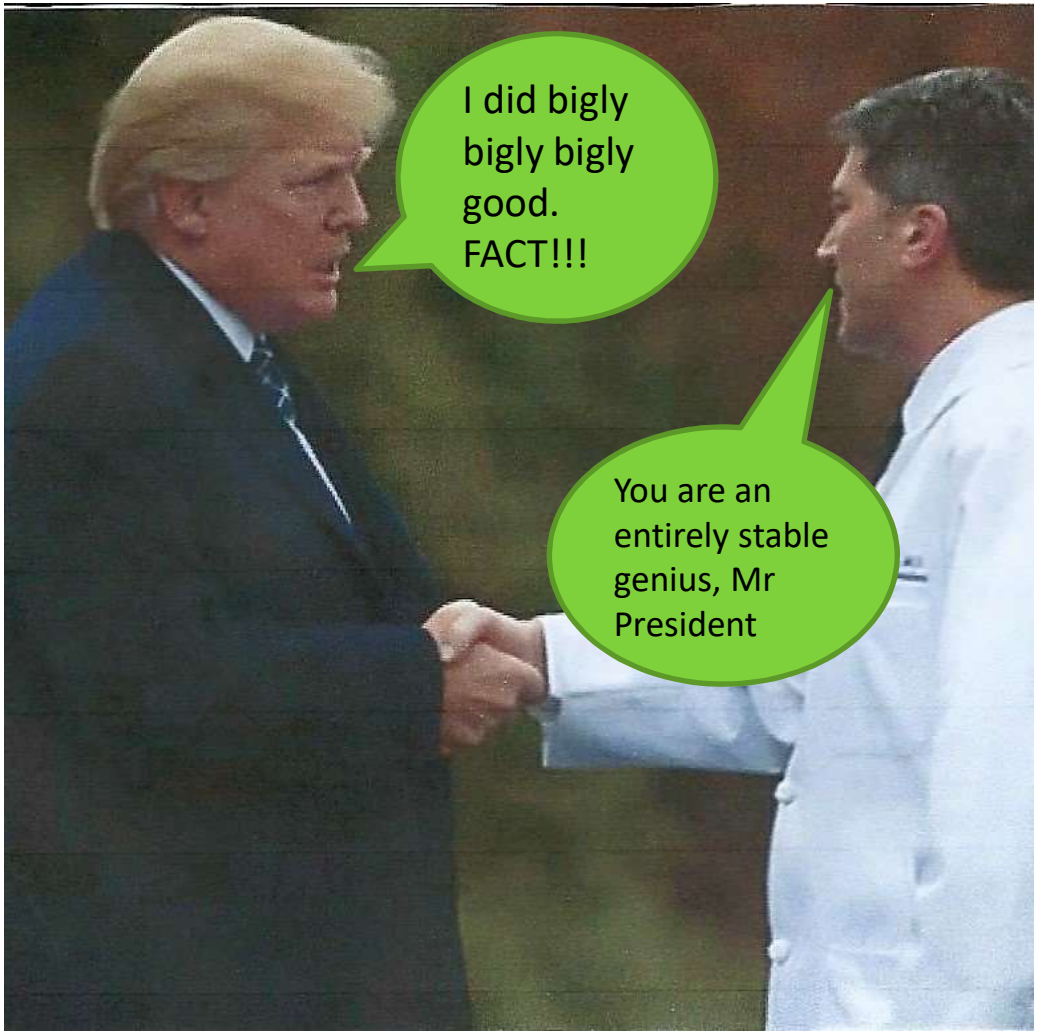
- *Primary Care and A & E*
  - GPcog (GP Assessment of Cognition)
  - ATMS (Abbreviated Mental Test Score)
- General physicians, Geriatricians, General neurologists
  - Folstein's Mini Mental State Examination - MMSE

Problems with MMSE

- Not applicable to some groups
- Over-dependent on verbal functions
- Insensitive to mild dementia

Comprehensive tests

- ACE-III (Addenbrookes Cognitive Examination v 3)
- MoCA (Montreal Cognitive Assessment)



"Examination of the cranial nerves, cerebellar function, deep tendon reflexes, motor function, and sensory system were all normal". A cognitive screening exam using the Montreal Cognitive Assessment was normal, with a score of 30/30".

Verbatim report by Admiral Dr Ronny Jackson – Guardian January 17th 2018

Diagnostic pathway - II

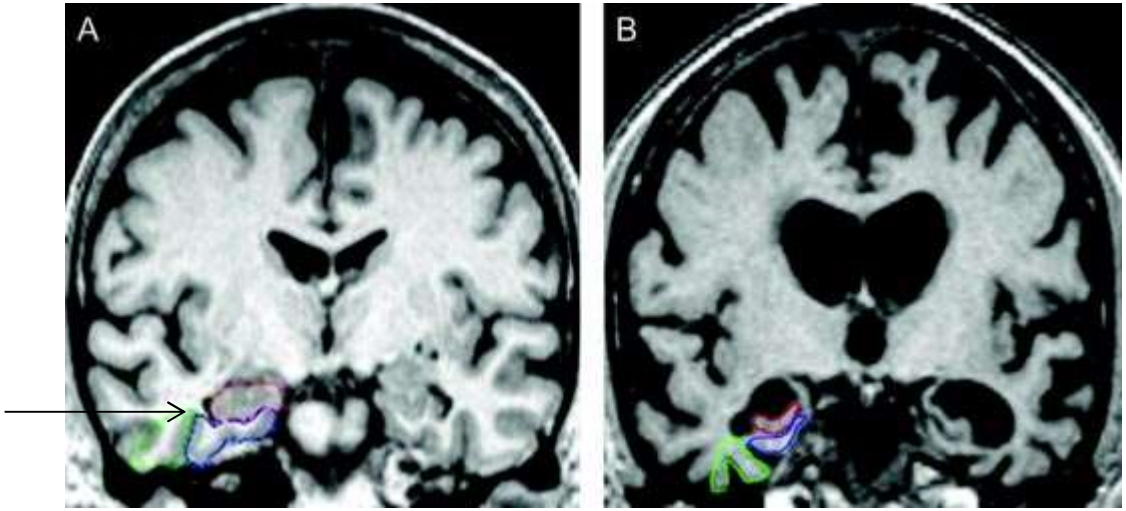
Laboratory investigation: What type of dementia?

1. Exclude treatable causes
    - *Hypothyroidism*
    - *B12 deficiency*
    - *Syphilis*
    - *Chronic Lyme disease*

2. Neuroimaging
    - *CT - intracranial mass lesions, hydrocephalus, subdurals, infarcts, atrophy*
    - *MRI – midbrain atrophy in 'parkinson plus' demyelination, small vessel disease*

Neuroimaging in Dementia

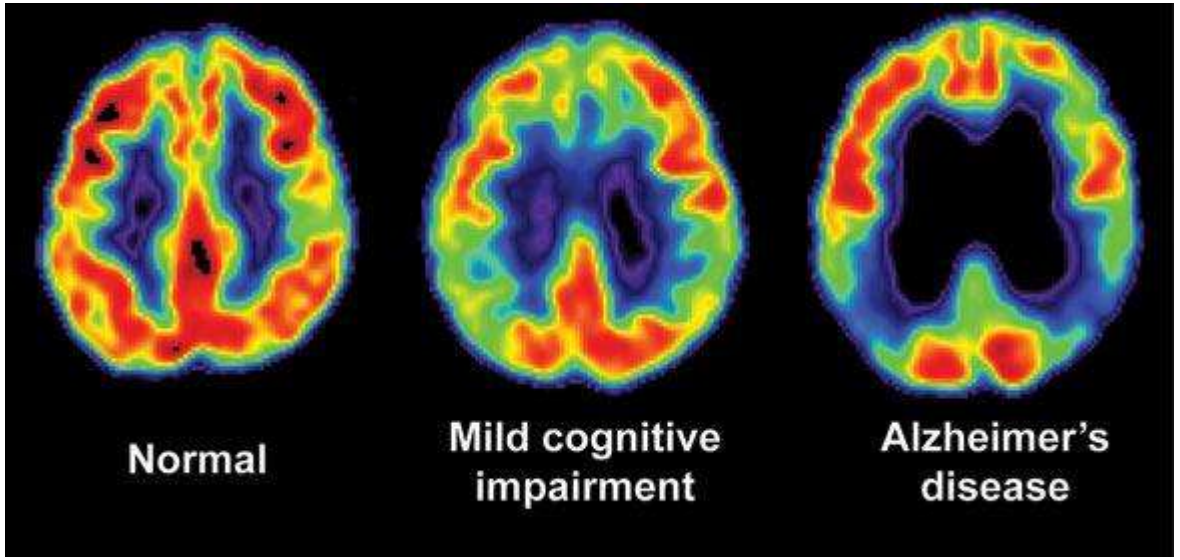
Normal aging



Alzheimer's Disease

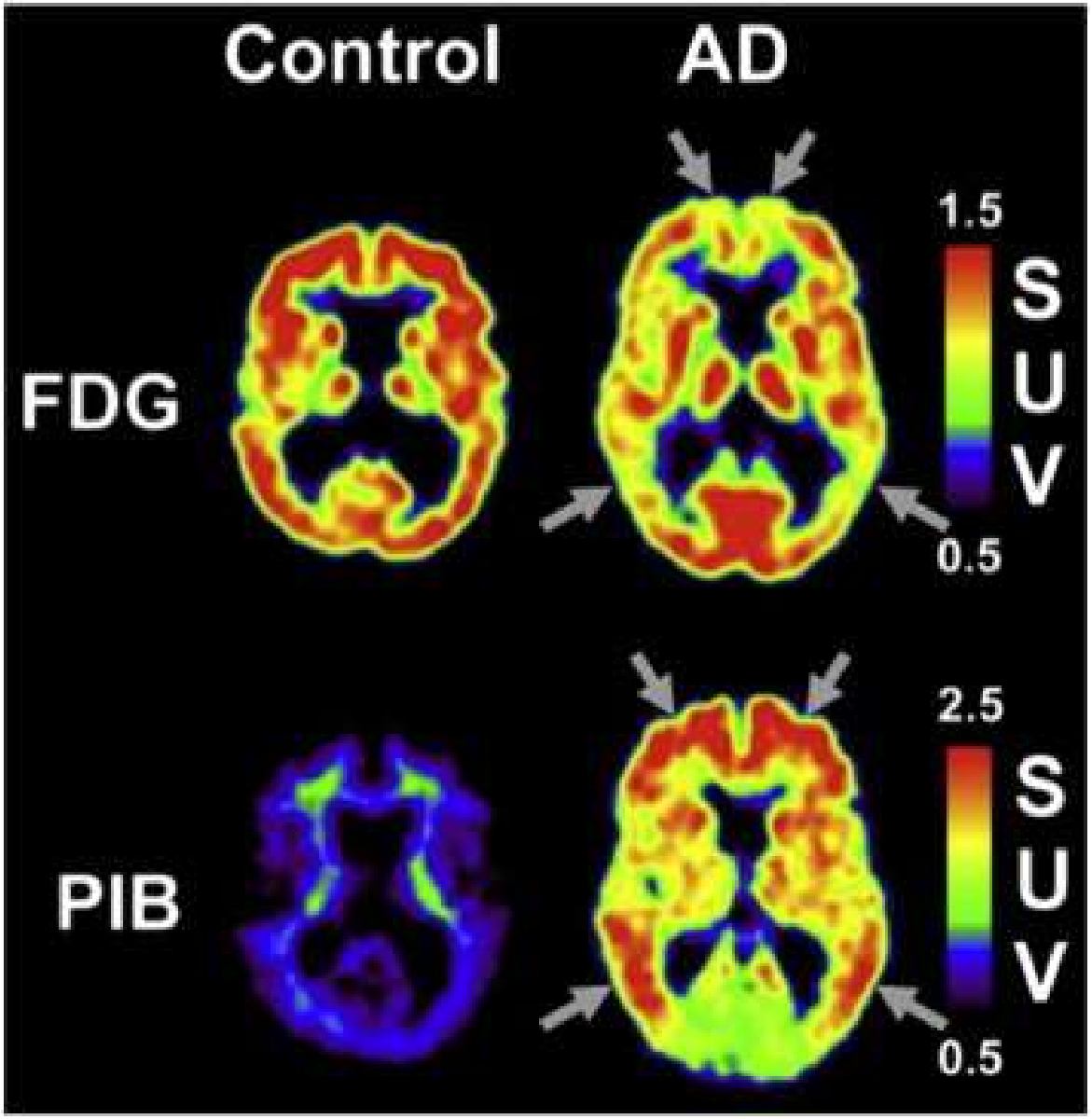
Normal temporal pole, hippocampus

Cerebral atrophy, hydrocephalus *ex vacuo*, temporal atrophy



FDG-PET Glucose metabolism

FDG-PiB PET imaging



Regions of cortical hypometabolism (FDG) in AD show strong uptake of the PiB amyloid biomarker (arrows)

Use of longer lasting ligands eg florbetapir. Plaque density and analysis of patterns of regional deposition may allow earlier diagnosis

CSF and blood biomarkers in dementia

CSF biomarkers

- Proteomics increasingly helpful in distinguishing
  - AD from MCI and normal aging
  - AD from other dementia pathologies

Seeburger et al. J Alz Dis 2015;44:525-39

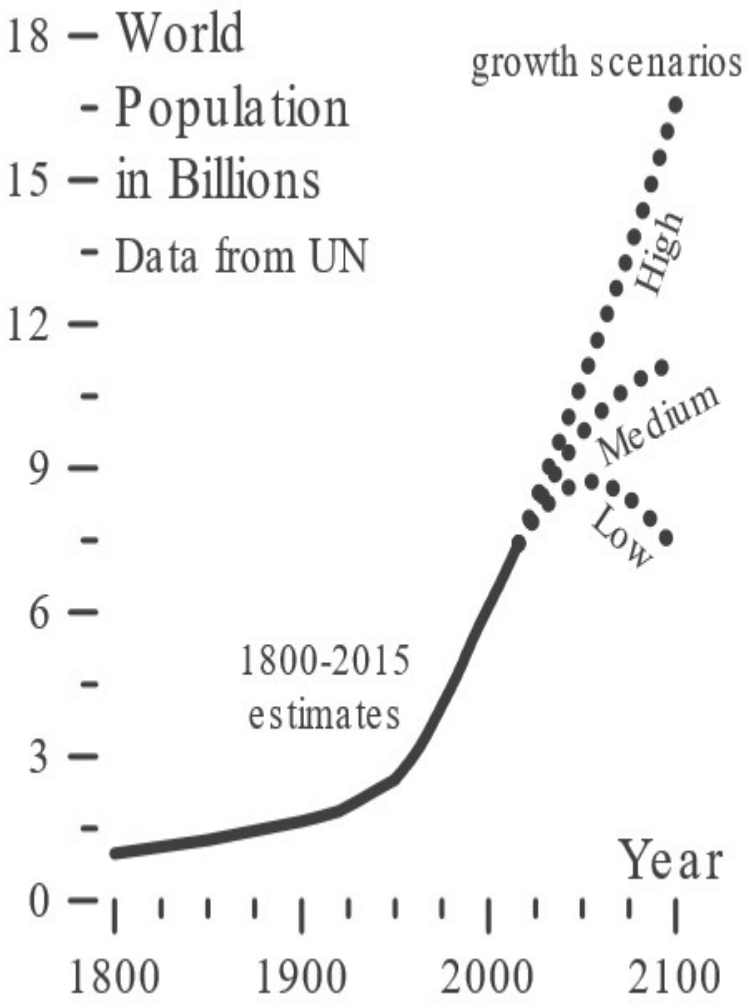
- Low Aβ42/tau fragment distinguishes AD from normal with 89% sensitivity and specificity across all published studies
- Intermediate results for MCI but lowest ratio cases typically progress to AD
- Also distinguishes AD from other dementia pathologies with 84 – 100% sensitivity and specificity

Blood biomarkers

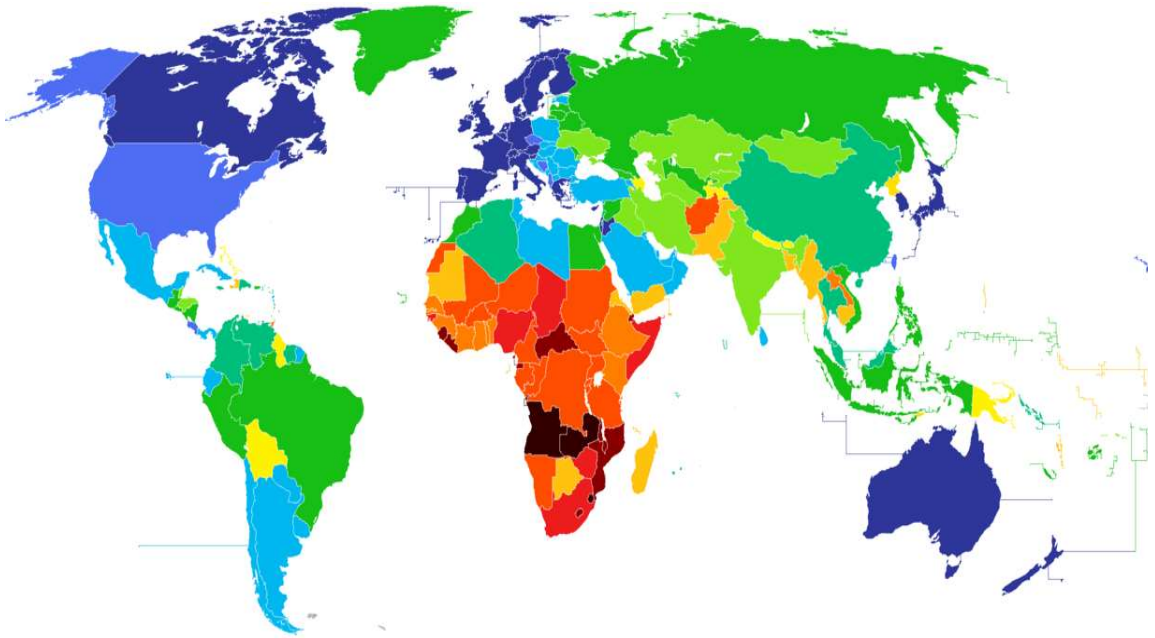
O'Bryant et al. Alz Dement 2016;3:83-90

21 microproteins

	PPV	NPV
AD	*80%*	*95%*
MCI	*74%*	*93%*
Neurodegen	*85%*	*94%*

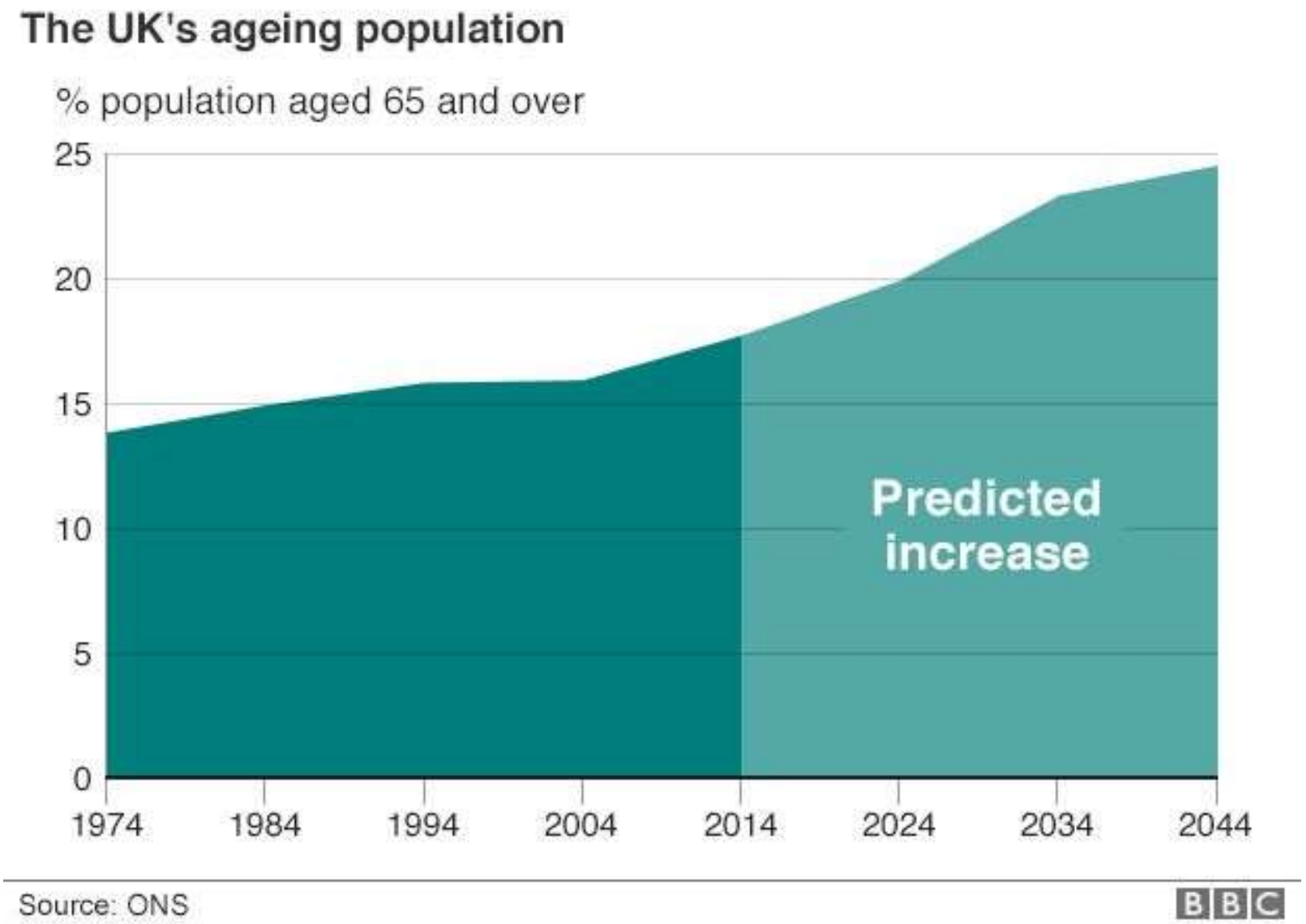


World population over time



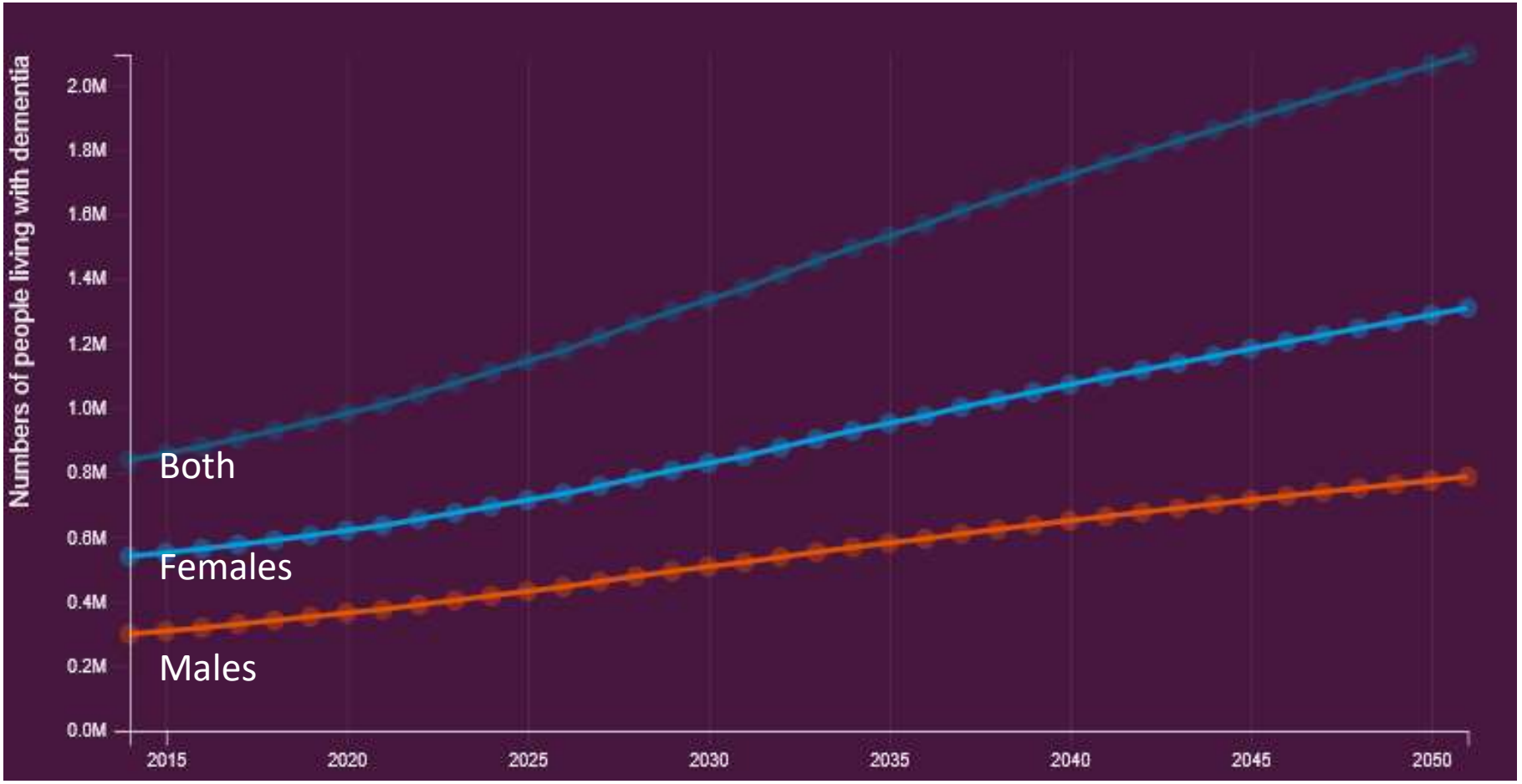
Mean age at death by country

Population Demographics



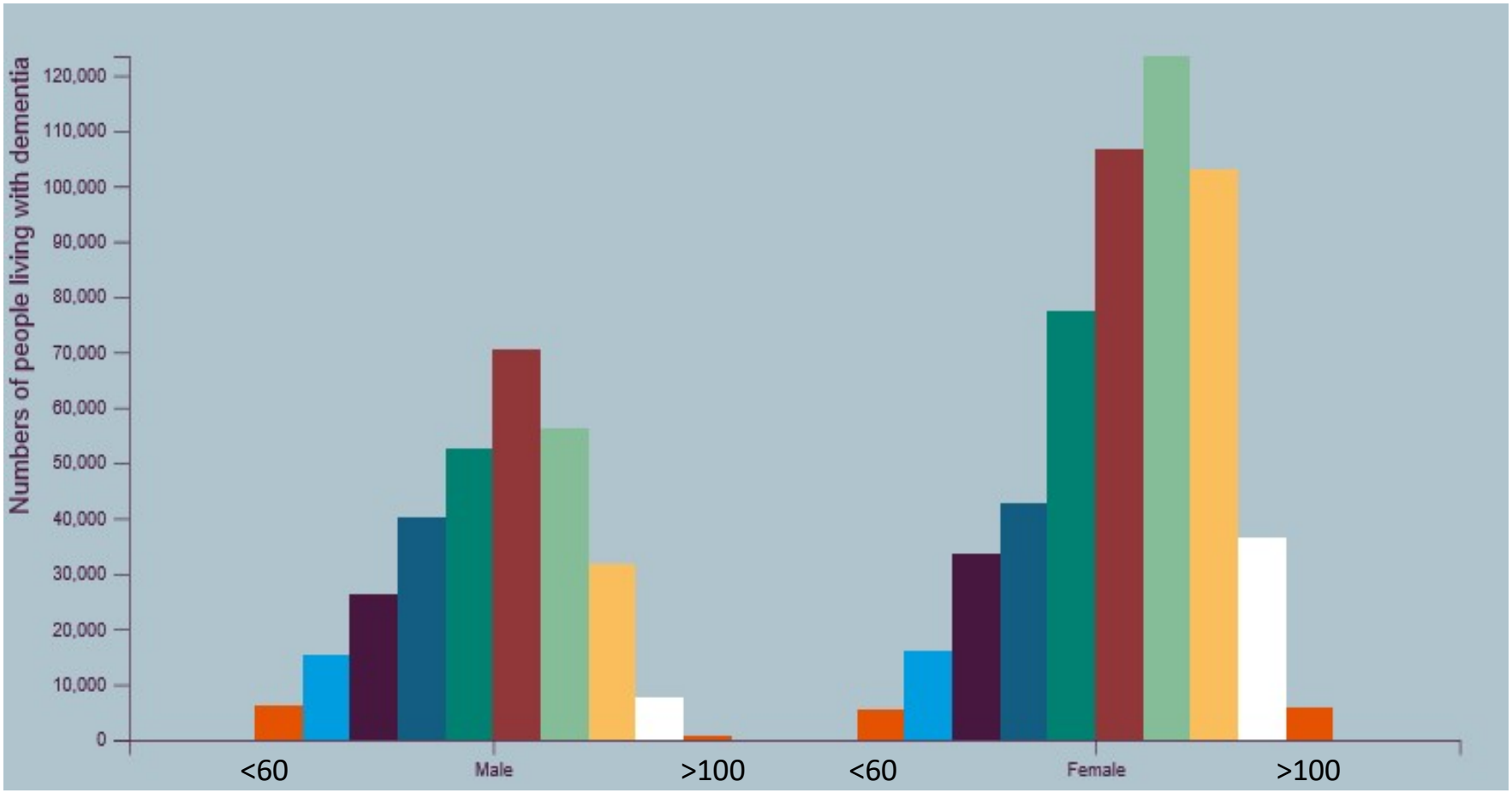
Conquest of infectious diseases
Better treatment of major trauma
Reduction in maternal and infant mortality

Blood pressure control
Reduction in smoking
Aspirin



Projections for dementia prevalence in UK to 2050

Will increase from 0.9 million to >2 million by 2050



Age related prevalence of dementia in the UK

5 year epochs from <60 - >100 years

- 65 million people in UK
- 850,000 people have dementia; 1 in 79 of the population and 1 in 14 over age 65
- 1 in 3 people born today will develop dementia
- Peak prevalence is between 80 and 90 years of age but can occur from 30
- *Decreases* in prevalence after age 90. *Not merely a function of aging.* **WHY?**
- Women affected significantly more often than men *at all ages.* **WHY?**

Risk factors for dementia

- **Family history** – Neurodegenerative diseases are genetically determined. 5 – 10% are inherited
- **Risk factors for vascular disease** are common to risk factors for dementia
- '**Brain Health**'- low educational achievement, mental illness, lack of 'cognitive activity'

Nine factors that contribute to the risk of dementia

***Alzheimer's Association. Presentation to Lancet Commission on dementia prevention, intervention and care* 2017**

- Mid-life hearing loss - 9% of the risk
- Failing to complete secondary education - 8%
- Smoking - 5%
- Failing to seek early treatment for depression - 4%
- Physical inactivity - 3%
- Social isolation - 2%
- High blood pressure - 2%
- Obesity - 1%
- Type 2 diabetes – 1%

Aging and dementia

Dementia is linked to aging but is not caused by aging

- Benign senescent forgetfulness, age associated memory impairment, age associated cognitive decline etc.

  MMSE between 29 and 25

Mild Cognitive Impairment (MCI)

- MCI is believed to affect 16 - 20% of the population.
  - *Cognitive symptoms, decline or impairment*
  - *Evidence of impairment in one or more cognitive domains*
    - *Amnestic MCI, non-amnestic MCI*
  - ***Functioning normally***
  - *Not demented. MMSE >19*
- 80% of MCI cases progress to dementia**, but *20% improve to normal*** although still at risk
  - Lower burden of risk factors
  - Higher baseline cognitive reserve from outset Super-agers are smarter!

Why is the prevalence of dementia greater in women ?

We don't really know. Not just because they live longer!

Higher prevalence at all ages

- Men and women are different!
  - Differences in particular cognitive faculties
    - e.g. Men better with spatial memory, women with verbal memory and object location
  - Differences in brain structure and associated sex hormone receptors
    - Men have larger amygdala and thalamus with more androgen receptors
    - Women have larger hippocampi with more oestrogen receptors

Hormone/receptor effects

- Effect of fluctuation and then loss of hormones and receptors more profound in women than men
- Estrogen in particular is neuroprotective. Loss reduces protection from amyloid plaque formation

Vascular disease

- Women at greater risk of obesity in middle age, hypertension, hyperlipidaemia, Type 2 diabetes

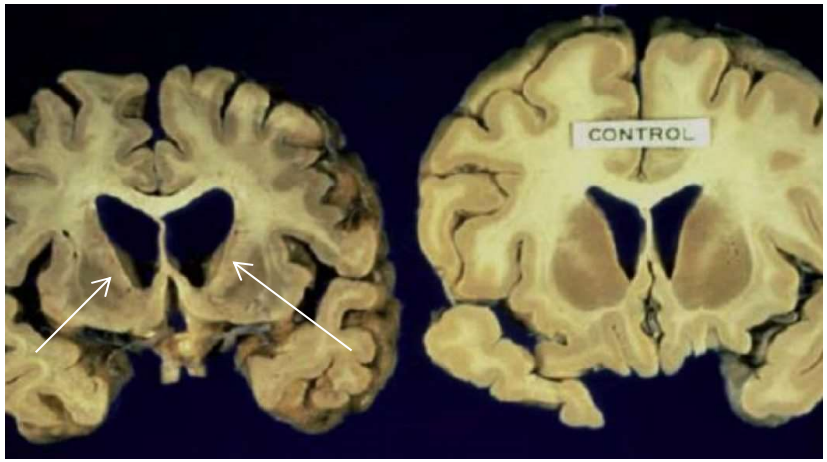
Treatment of dementia

(*viz*. brain disease related dysfunction)

- A few rare causes of dementia are treatable
  - Hypothyroidism, B12 deficiency, some infections, some immunological diseases, benign brain lesions eg some tumours, SDH, NPH
- Treatments for dementia related symptoms

  Memory impairment is partly due to loss of central ACh
  - Centrally acting anticholinesterases. Increase brain ACh
    - donepezil, rivastigmine, galantamine (*early mild dementia*)
  - NMDA antagonists
    - memantine (*moderate to severe dementia*)
- **Otherwise, we have no way of preventing, curing or halting the progression of common forms of dementia**
  - Anti- βamyloid immunisation trials negative to date

Gene silencing in Huntington's disease



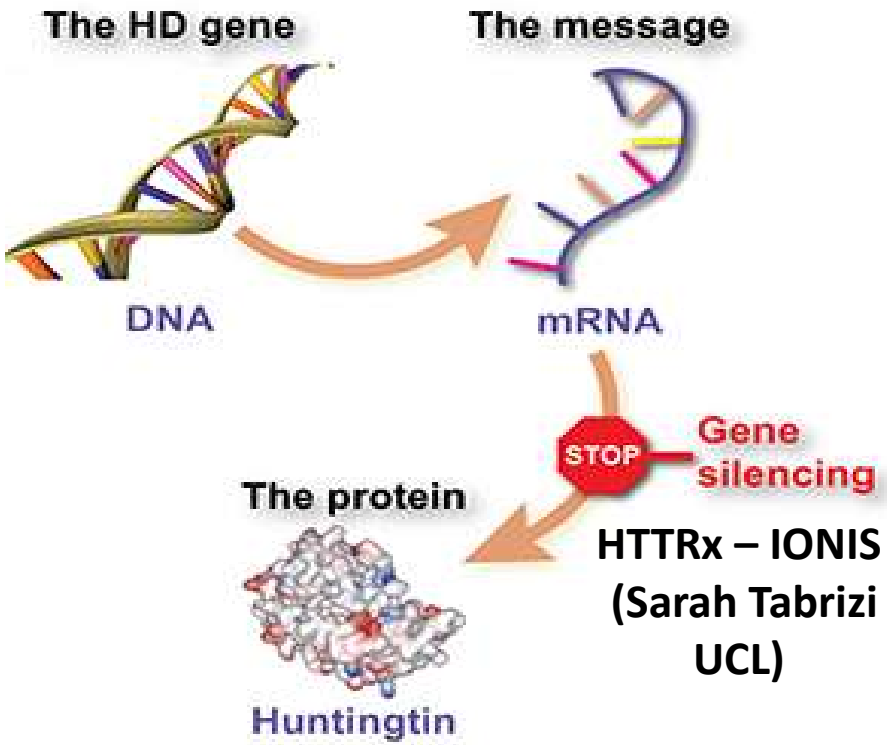
Progressive and fatal disease characterised by severe, violent involuntary movements (*chorea*) and dementia

Autosomal dominant

Caused by a mutation in *huntingtin* gene on Chr 4.

Accumulation of abnormal huntingtin protein in basal ganglia neurones. Frontal and basal ganglia atrophy

- Single gene disease
- Toxic 'gain of function'
- *translation of mutant mRNA blocked by anti-sense oligonucleotides in mice*



HTTRx – IONIS (Sarah Tabrizi UCL)

A MIRACLE??

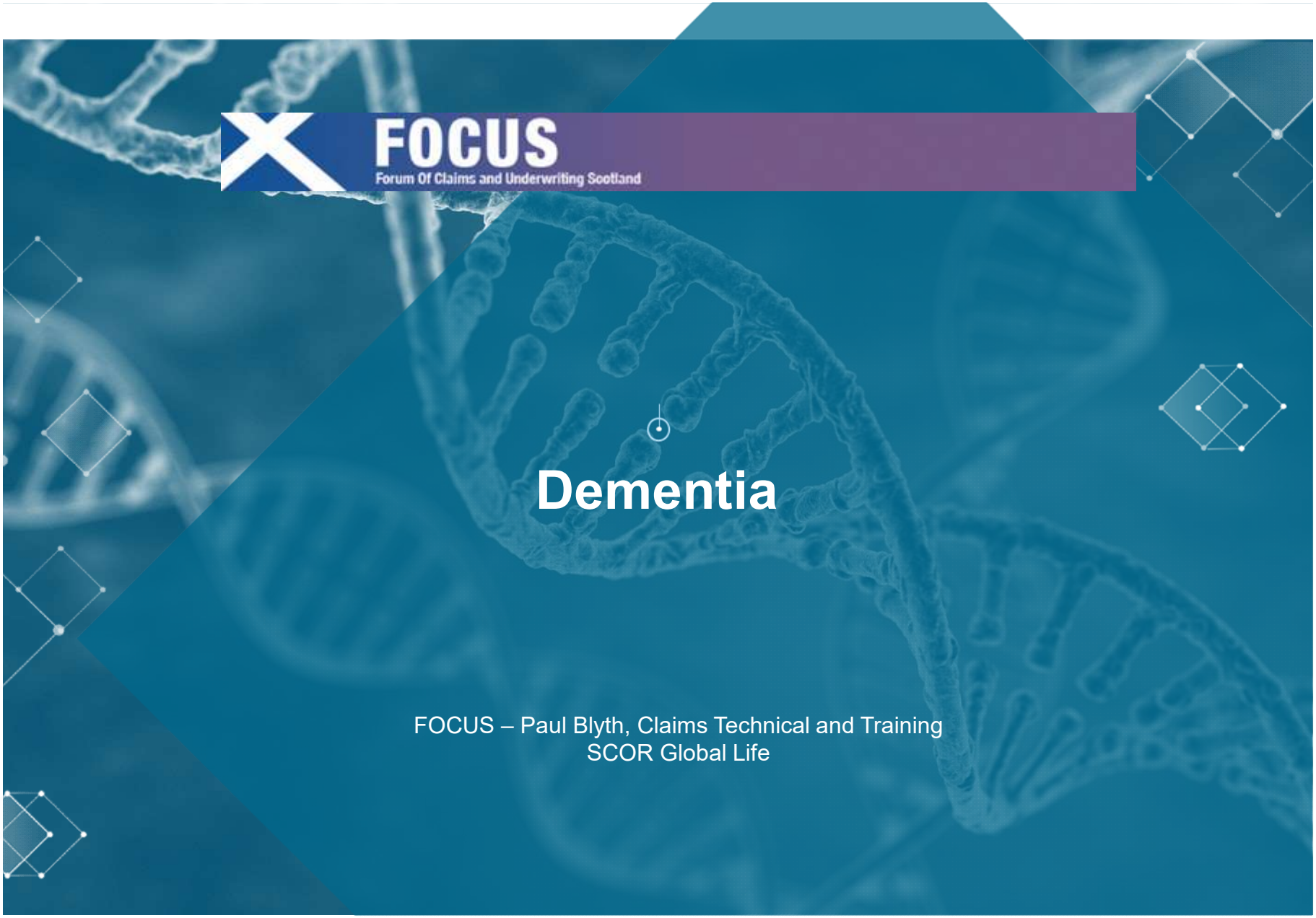
Summary

You should now be able to

- Define the term ‘dementia’ and relate how this word came into being
- Explain how dementia differs from Alzheimer’s disease
- Differentiate between the common ‘primary’ dementias from diseases in which dementia occurs as a consequence
- State the most common types of dementia and how they present
- Know how dementia is diagnosed
- Point out the key risk factors for dementia
- Describe ‘senility’ and ‘mild cognitive impairment’ and how they differ from dementia
- Know what treatments claimants with dementia might be using and why

FINALLY - some advice to avoid dementia

- Choose your parents carefully
- Lead a simple, quiet, studious life
- Diet! Exercise!
- Protect your blood vessels

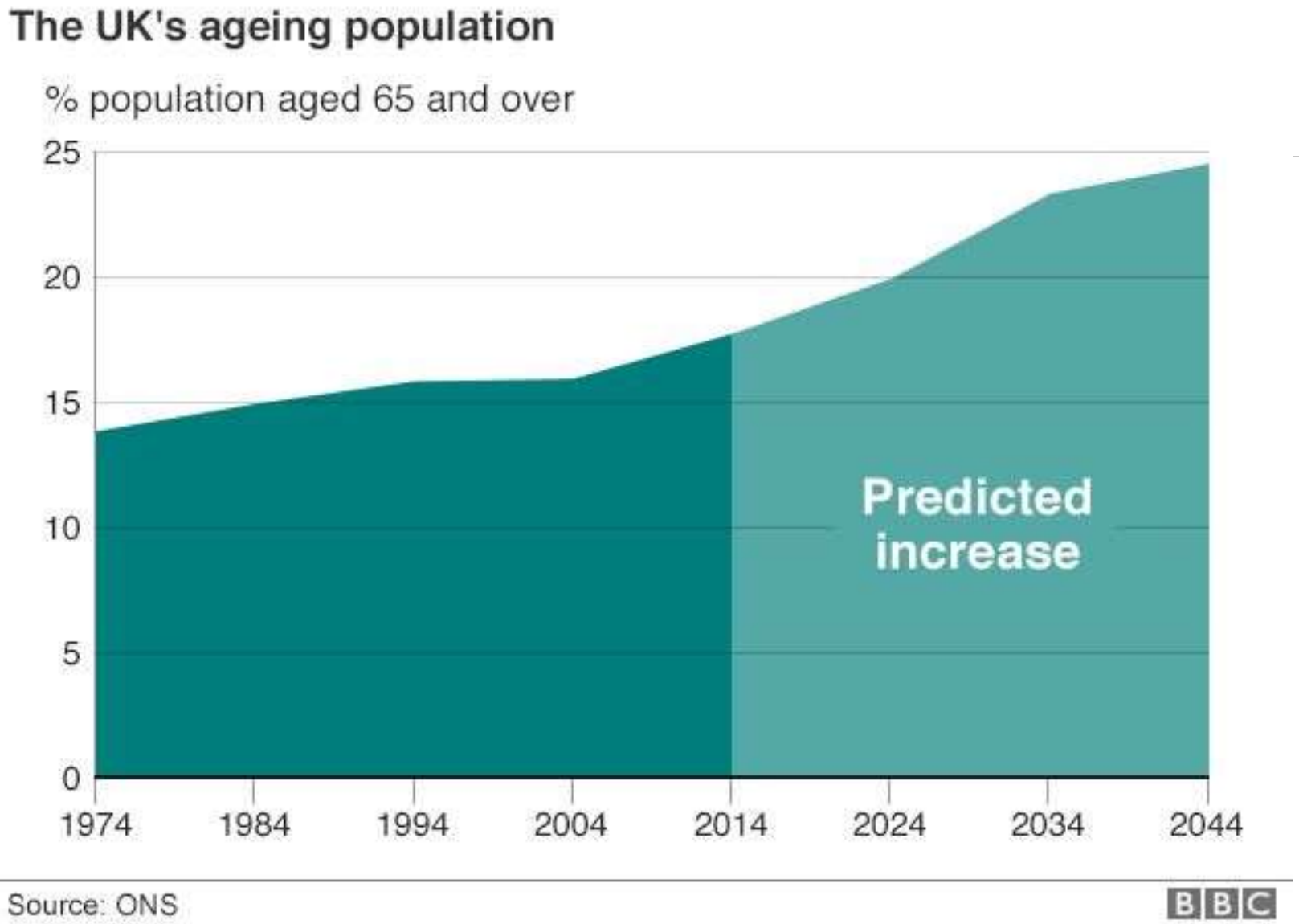


Dementia

FOCUS – Paul Blyth, Claims Technical and Training
SCOR Global Life

SCOR The Art & Science of Risk | Life

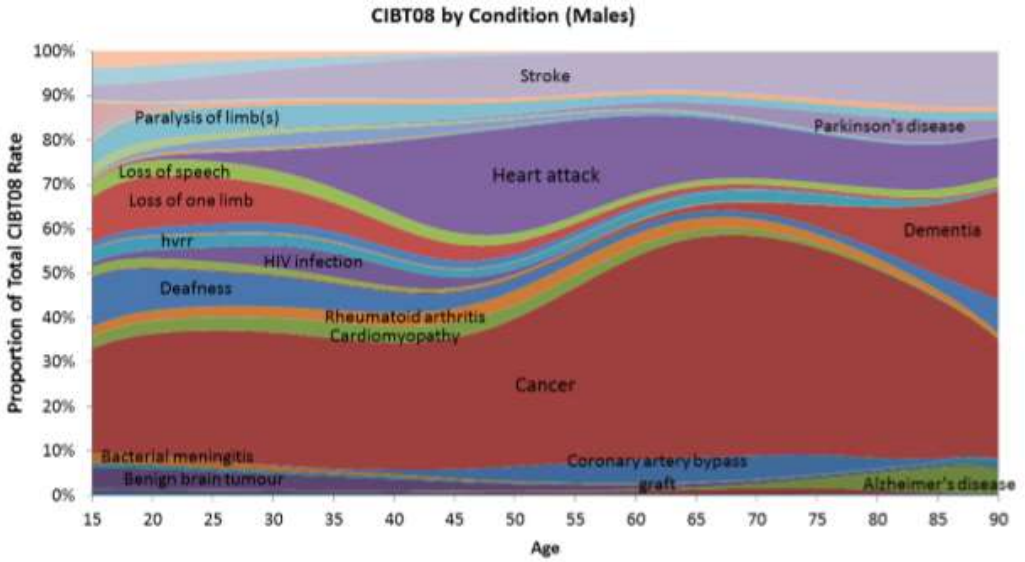
The reality of dementia

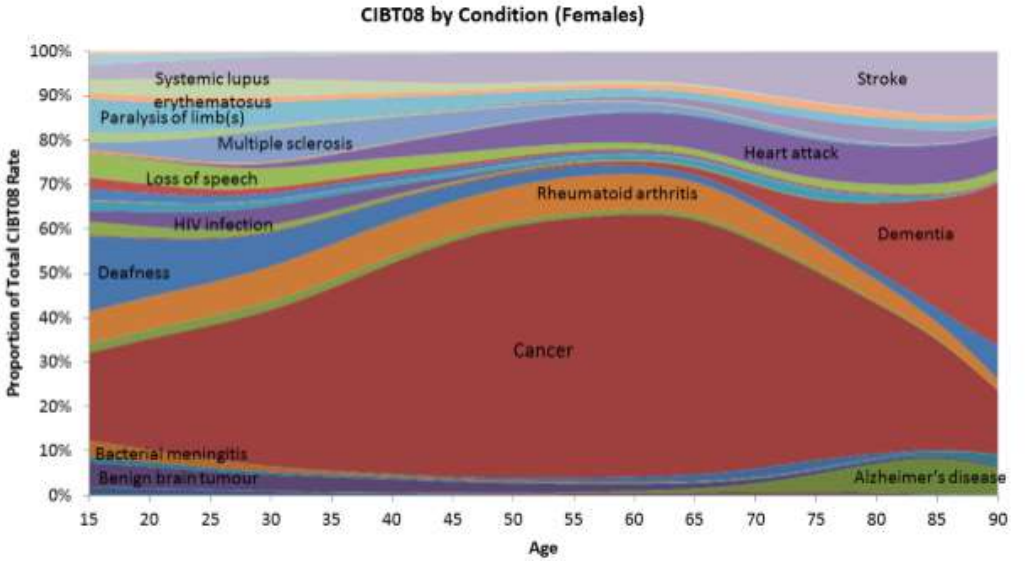


Conquest of infectious diseases
Better treatment of major trauma
Reduction in maternal and infant mortality

Blood pressure control
Reduction in smoking
Aspirin

Disease trend by age





SIAS
Staple Inn Actuarial Society

Extending the Critical Path

A report from the Critical Illness Definitions and Geographical Variations Working Party

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Presented to The Staple Inn Actuarial Society

Staple Inn

3rd December 2013

SCOR The Art & Science of Risk | Life

ABI model wording for Alzheimer's disease

2006, 2011 and 2014 ABI Statement of Best Practice

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.

Other “Dementia” definitions in the market

PRE SENILE DEMENTIA BEFORE AGE 65 (DEMENTIA)

A diagnosis, before the 65th birthday of the Life Assured, by a consultant neurologist holding an appointment in a hospital in the UK or Republic of Ireland of pre senile dementia such as that caused by Alzheimer’s disease.

The diagnosis must, at the time it is made, be supported by evidence of progressive deterioration of memory and of the ability to reason and to perceive, understand, express and give effect to ideas.

Moving towards……..

Dementia, including Alzheimer's disease, resulting in permanent symptoms

(a) A definite diagnosis of Dementia including Alzheimer's disease by a Consultant Neurologist, Psychiatrist or Geriatrician.

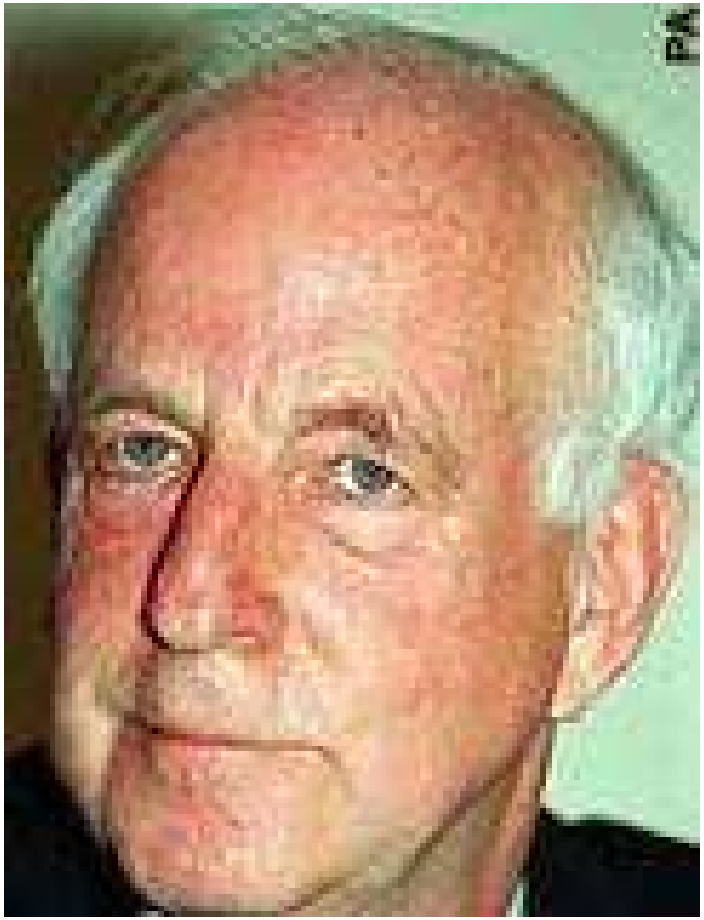
(b) There must be permanent clinical loss of the ability to do all of the following:

  (i) remember

  (ii) reason, and

  (iii) perceive, understand, express and give effect to ideas.

Benefits for severity criteria



Pathology of Dementia

- *Alzheimer's disease (AD)*
  - Temperoparietal. Memory loss
  - Focal lobar atrophy. Dysphasia, cortical visual loss
- *Vascular dementia (VaD)*
  - Arteriosclerotic – aging, hypoperfusion. Global, slow
  - Multi-infarct dementia – step-wise deterioration, strokes, multifocal
- *Dementia with Lewy bodies (DLB)*
  - Parkinson's disease (synucleinopathy)
  - Parkinsonian syndromes: MSA, PSP, CBD, (tauopathies), HD
- *Frontotemporal dementia (FTD)*
  - Various pathologies – AD, Pick's, TDP43, association with MND
- *Others*:
  - CJD (prion disease)
  - CTE (dementia pugilistica)
  - Drugs and alcohol
  - HIV encephalitis
  - Intracranial mass lesions
  - Etc.

Future Proofing?

When in Rome Aside from the serious business of Brexit, Theresa May enjoyed a lighter moment with her Italian counterpart, Matteo Renzi, in Rilly yesterday. Page 6

Scientists create the first drug to halt Alzheimer's

● Brain deterioration stopped by twice-a-day pill ● 'Wonderful' discovery raises glimmer of hope

Chris Smyth Health Editor

The Telegraph

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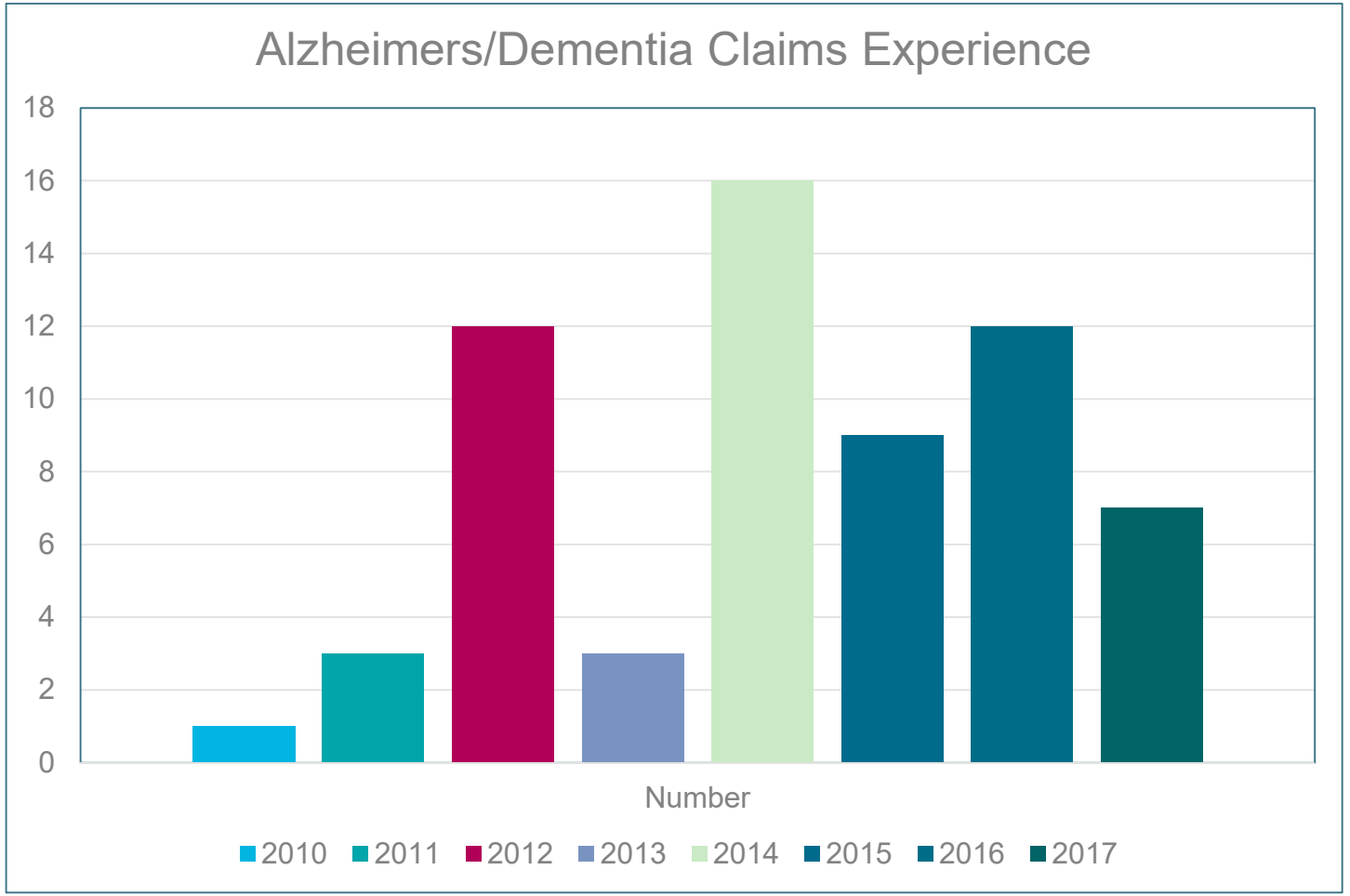
Blood test for ageing will predict dementia

Oliver Moody Science Correspondent

Test can predict Alzheimer's

By Sarah Knapton, SCIENCE EDITOR

Claims Stats



** Figures do not include incurred but not reported claim adjustments*

Conclusions

- More and more people will be diagnosed with a dementia due to an ageing population.
- Dementia/Alzheimers disease is not currently a common cause of claim. Therefore, the severity criteria is extremely important to future proof definitions and ensure there is a reasonable severity level worthy of a CI payment.
- Without this criteria, potentially we could see far more claims for very early signs of forgetfulness/confusion
- Potentially conditions such as Alzheimer’s disease can be diagnosed AND treated prior to becoming symptomatic
- Positive move on the definitions combining Alzheimer's and Dementia
  - Sensible to combine definitions together making it easier for consumers to understand
  - Moves away from making Critical Illness a “numbers” game
  - Meets approval from stakeholders including the like of CI Expert and Defaqto

Questions?