Living well to prevent dementia and beyond

Dr Matthew Kinchington

Geriatrician and Senior Lecturer UNSW Rural clinical school

aims

- Demography
- What is Dementia and MCI
- Risk factors
- Preventative approaches
- Current clinical trials

Figure 3. Projected incidence of dementia in NSW by gender, 2010-2050.[9]

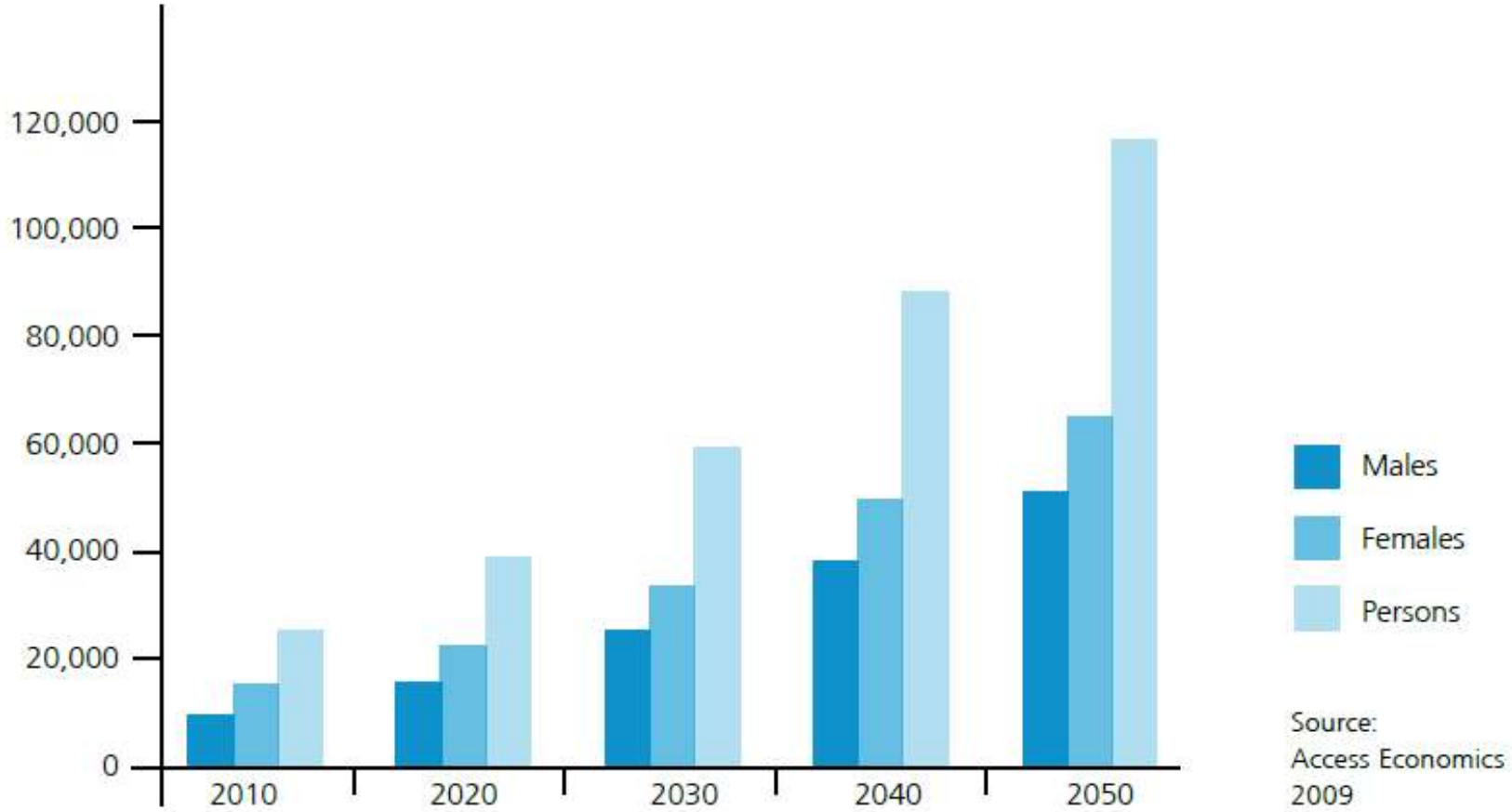
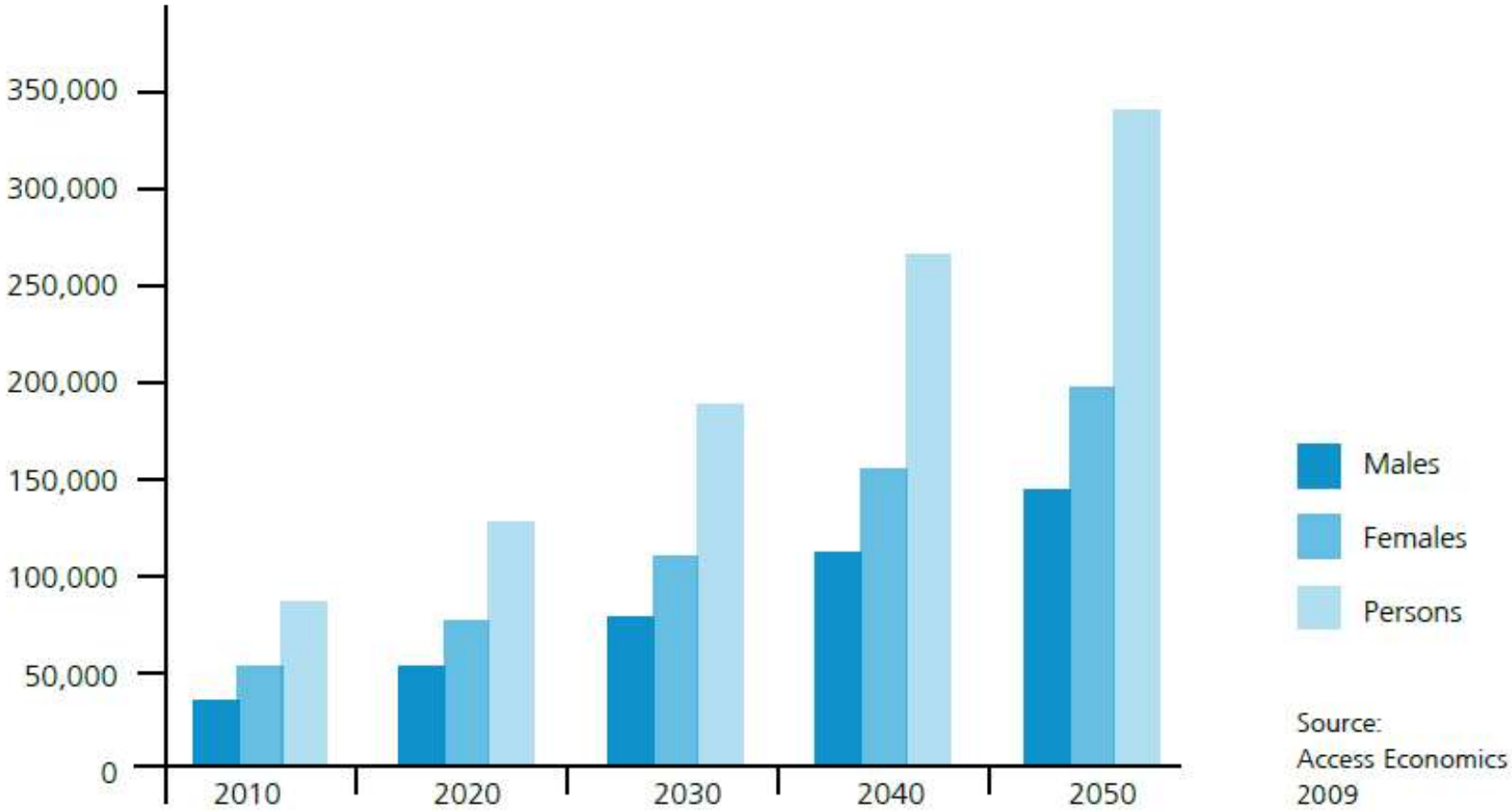
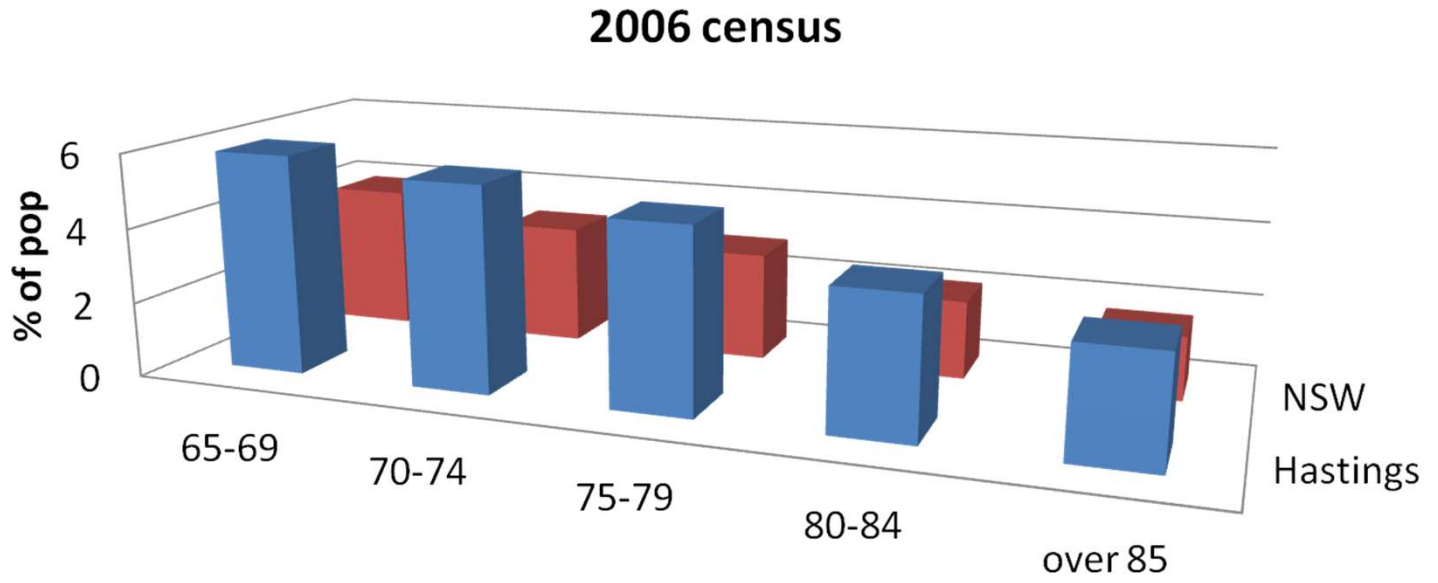


Figure 2. Projected prevalence of dementia in NSW by gender, 2010-2050.[9]



Comparison of populations



	65-69	70-74	75-79	80-84	over 85
Hastings	5.9	5.5	4.9	3.7	2.9
NSW	3.9	3.2	2.9	2.1	1.7

Burden of disease

- $820 Billion USD, with 47mil people
- 85% costs attributable to social factors and family costs
- Incidence and prevalence data varies around the world
- Generally stabilising in wealthier countries
- Focus on risk factors
  - Delay onset
  - Reduce costs to society
  - Need to be modifiable.

demography

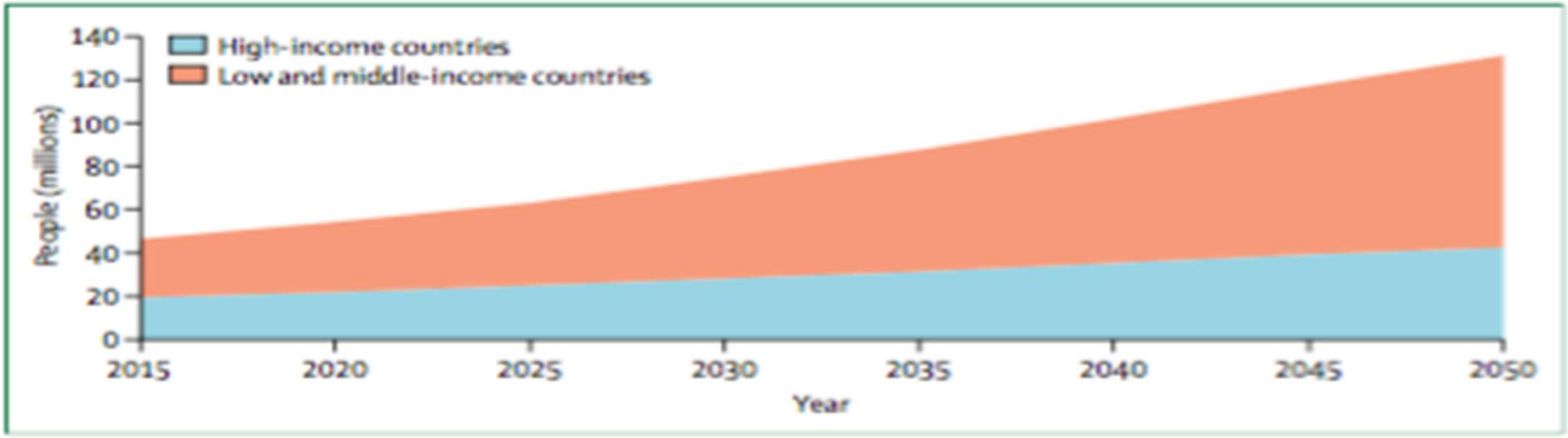
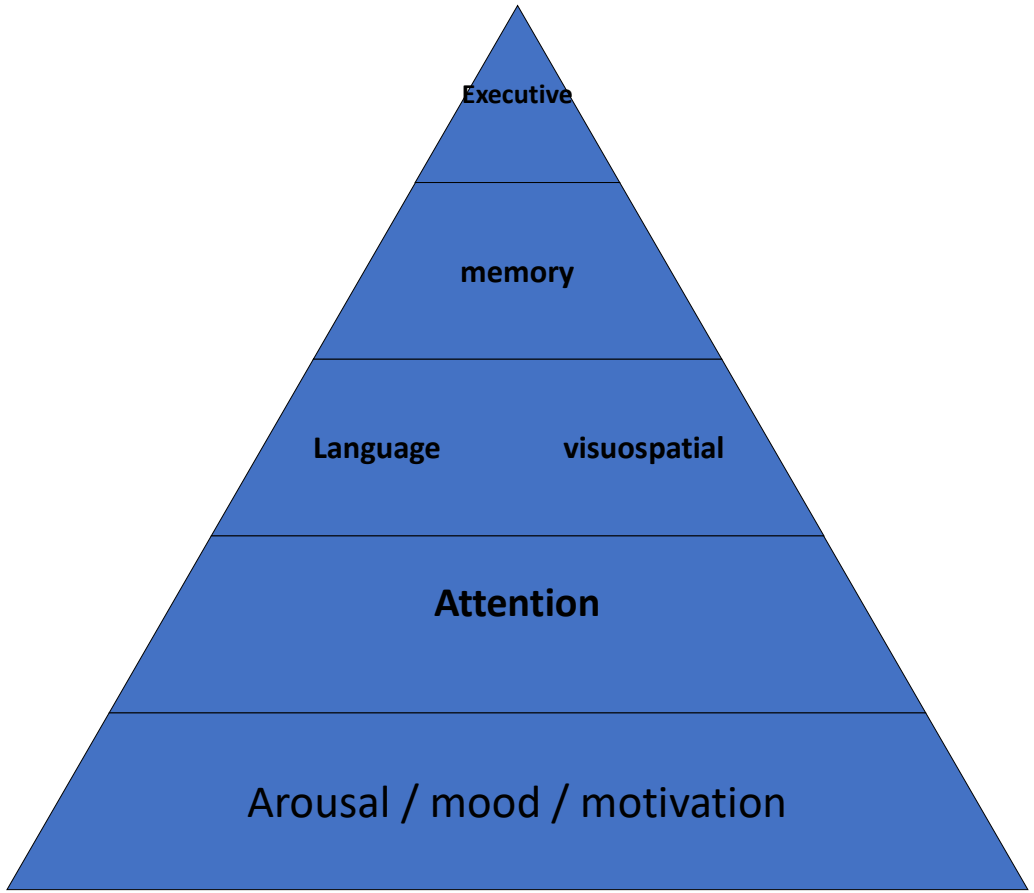


Figure 1: **Growth in numbers of people with dementia in high-income and low and middle-income countries**
Reproduced from Prince and colleagues,[2] by permission of Alzheimer's Disease International.

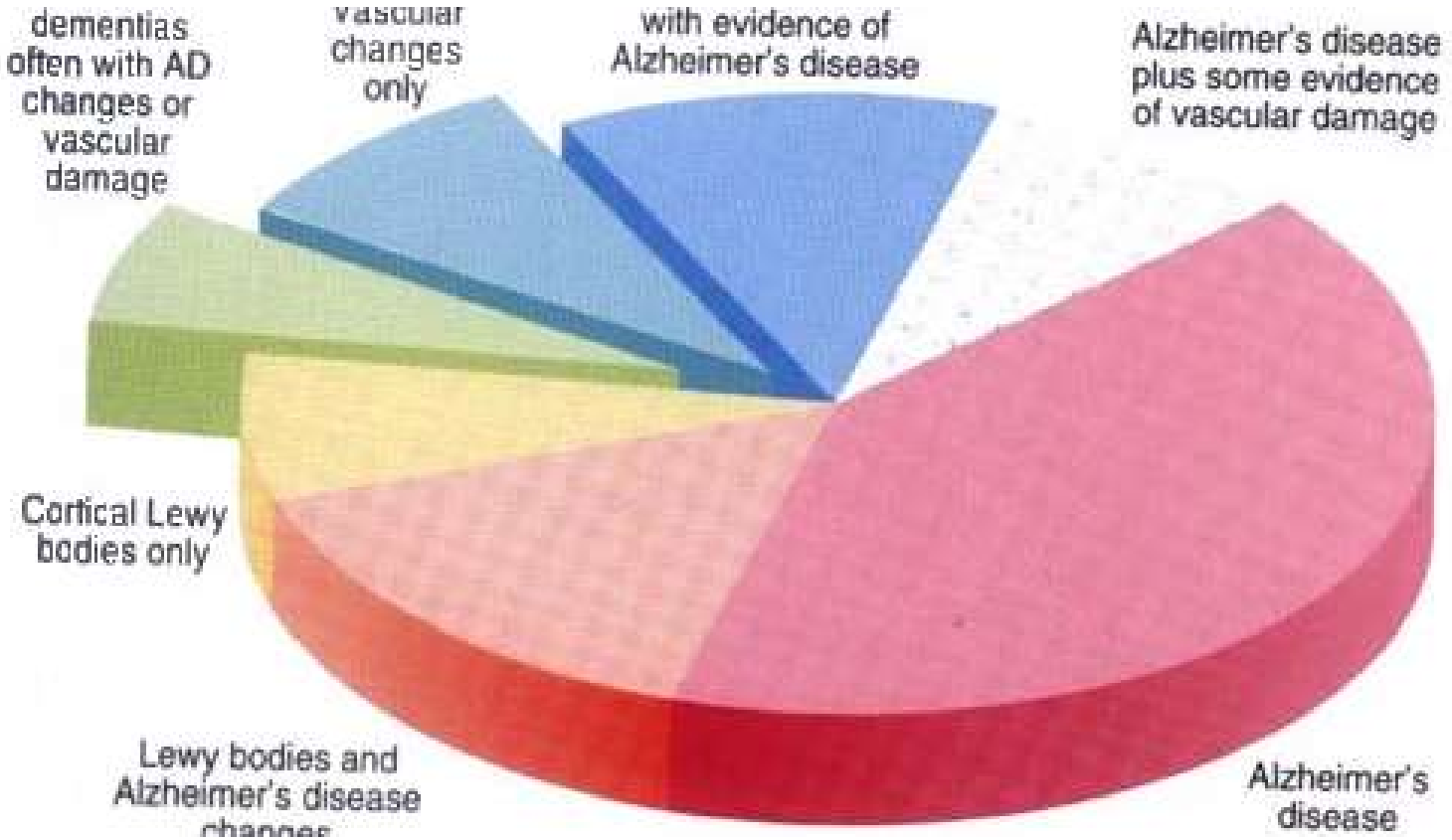
Concepts

- Mild cognitive impairment (20% >65yo)
  - Mild neurocognitive disorder
  - May precede Dementia
  - Potential for interventions
- Dementia
  - Major Neurocognitive disorder (DSM 5)
  - Decline in cognitive performance from a previously attained level, associated with significant functional decline


Executive
memory
Language
visuospatial
Attention
Arousal / mood / motivation

causes

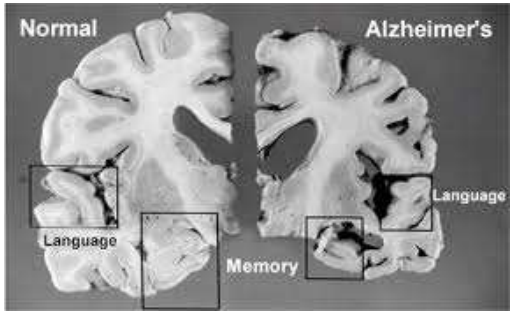
- Alzheimer's disease
- Mixed dementia
- Vasc cognitive impairment
- DLB/PDD
- FTD
  - Behavioural variant
  - Progressive primary aphasia
  - Semantic
- alcohol
- Non progressive cognitive impairment
  - Trauma, substance abuse
- Huntington's, wilson's, channelopathy
- Infections- HIV, CJD
- Autoimmune- vasculitis

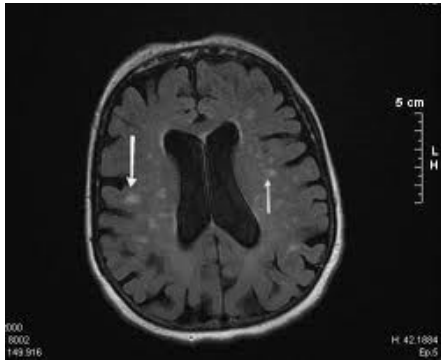

dementias often with AD changes or vascular damage
vascular changes only
with evidence of Alzheimer's disease
Alzheimer's disease plus some evidence of vascular damage
Cortical Lewy bodies only
Lewy bodies and Alzheimer's disease
Alzheimer's disease

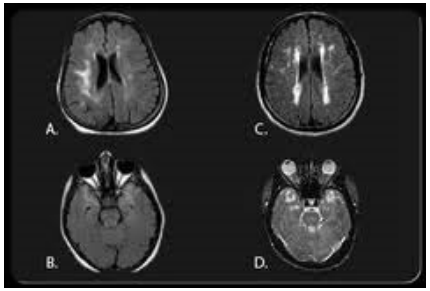
Pathological basis

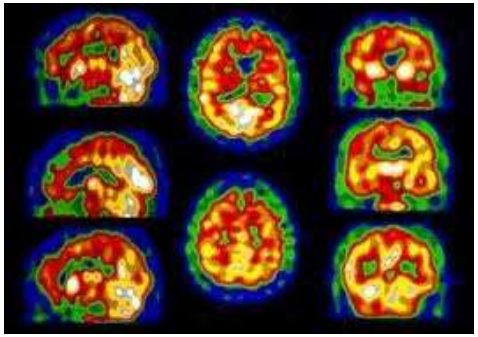
- Vascular disease
  - Brain injury due to large vessel strokes and small vessel occlusions
  - White matter microvascular disease
  - Present in older population
- Neurodegeneration
  - Plaques and tangles, Aβ in AD
  - Lewy bodies in DLB/PDD
  - Tau in FTD/AD

Different dementias









Cognitive reserve hypothesis

- Idea of resilience- ageing brain
- Based on autopsy studies
  - Cognitively normal people have pathological changes- AD +/- vasc Disease
  - Able to tolerate this burden without developing dementia or delay onset till later in life
- Reserve is due to:
  - Anatomical substrate or adaptability of cognition
  - Less reserve earlier development of dementia
  - There are factors that reduce or increase this

Ageing, AD and Cognitive deficits

- Ageing is the gradual change in an organism that leads to increased risk of weakness, disease and death (Webster thesaurus)
- For the brain:
  - ↓ size, neurotransmitters, receptor alteration
  - Loss of dendrites, electrophysiological change
  - Increased activation of microglial cells and changes in innate immunity
- Results in cognitive decline in multiple domains

Microglia in CNS

Front Aging Neurosci. 2017; 9: 175.

- 5 – 20% of total brain cells
- Highly plastic and significant variations in density
- Change function according to needs
  - Quiescent versus activated
- Pathological ‘stress’ stimulates activation:
  - Become mobile, phagocytic, release cytokines
  - M1 and M2

microglia

- M1
  - Pro-inflammatory
  - Neurotoxic (IFN-γ, TNF, IL-1, NO)
  - Inhibit proliferation of Lymphocytes
- M2
  - Repair damage, trophic support and anti-inflammatory via IL-3 and 4
  - a,b and c types

Role of microglia in neuronal life and death

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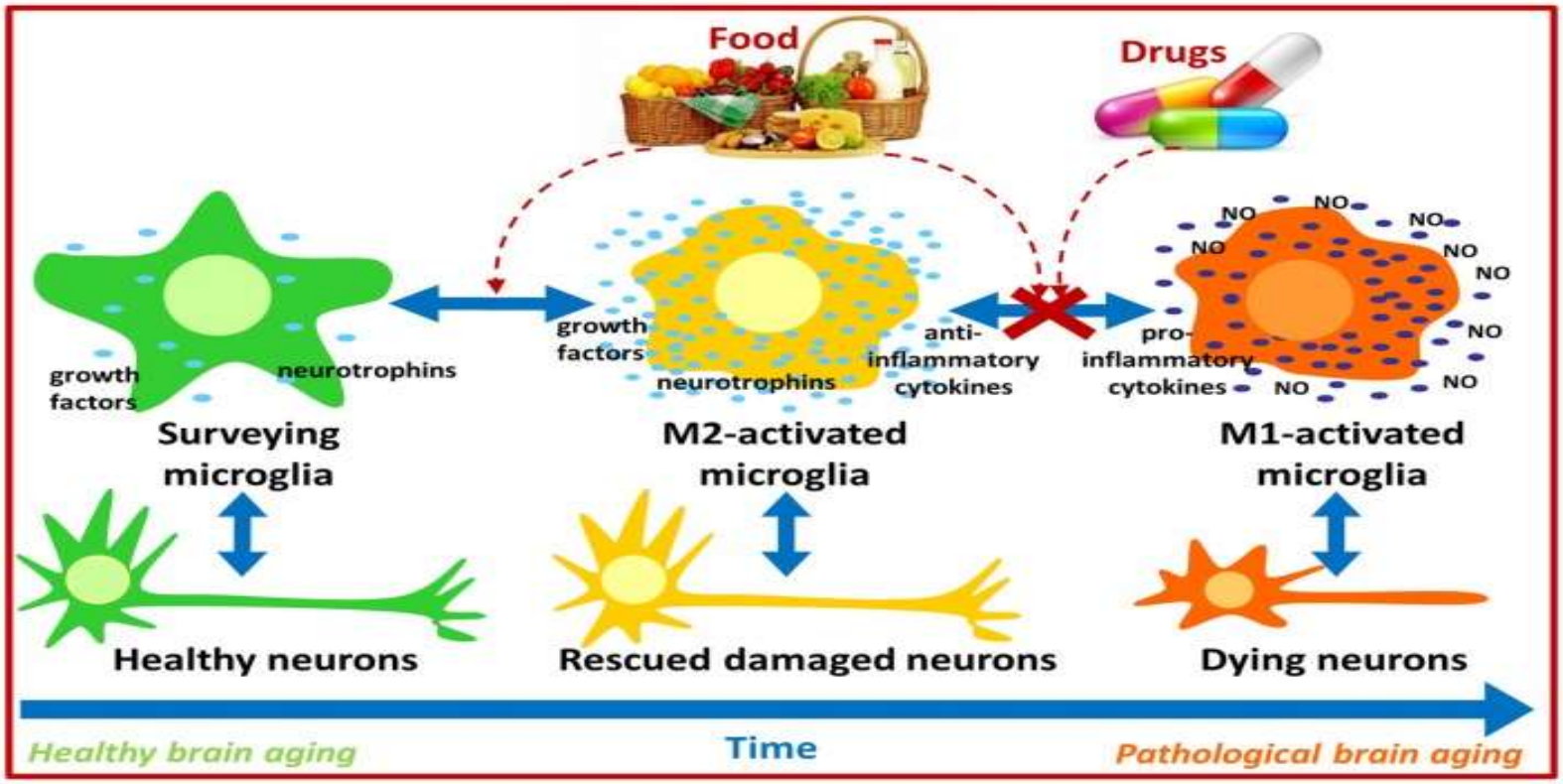


Factors that effect reserve

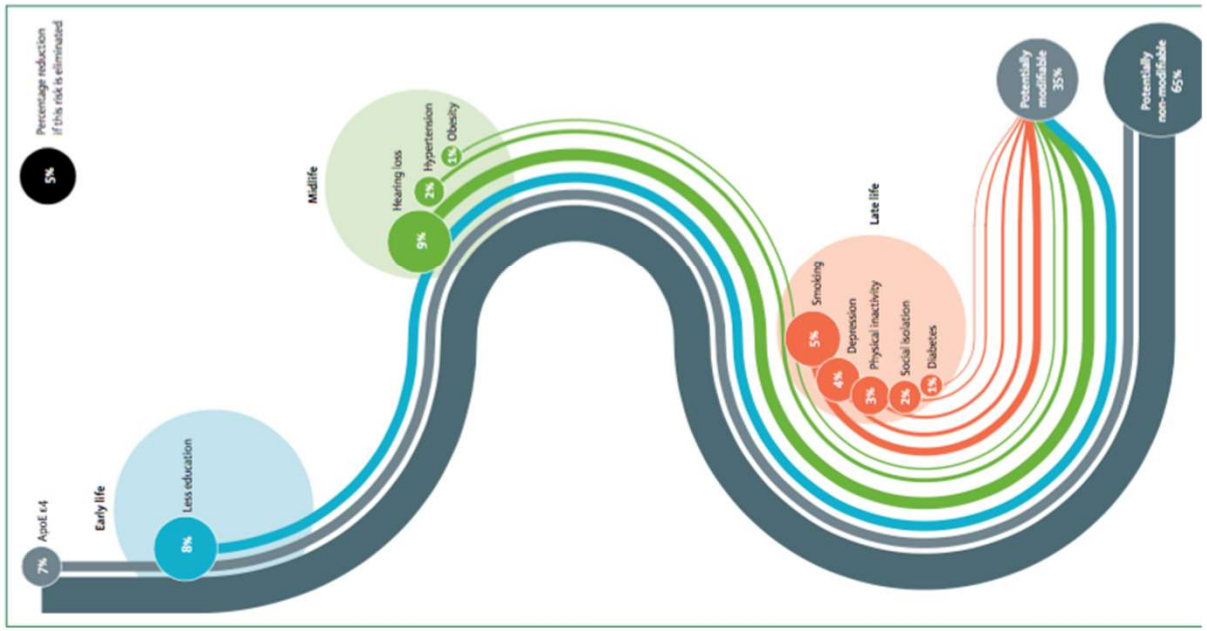
- Age- not modifiable, reduces reserve
- Genetics- not modifiable
  - Complex, risk promoting genes eg Apo E4
  - Rare <2% dominant inheritance :PS-1 and 2
- Incidence studies in western countries:
  - better lifestyle less dementia
  - Greater resilience with better education
  - Early childhood experience very important

Risk factors

- Up to 35% of dementia cases attributable to modifiable risk factors
- Age bands:
  - Early life <45
  - mid life 45-65
  - Later life >65 yo

Risk Factors through the lifecycle

http://dx.doi.org/10.1016/ S0140-6736(17)31363-6



Risk Factors

Common and modifiable

- Education
- Hearing loss
- Hypertension
- Obesity/poor diet
- Smoking
- Depression
- Physical inactivity
- Social isolation
- Diabetes

Less strong associations

- Head injury?
  - Single no
  - CTE- yes
- Visual impairment
- Sleep disorders
- Bilingual
- Air pollution
- Alcohol- linked

Risk Factors for development of dementia

http://dx.doi.org/10.1016/ S0140-6736(17)31363-6

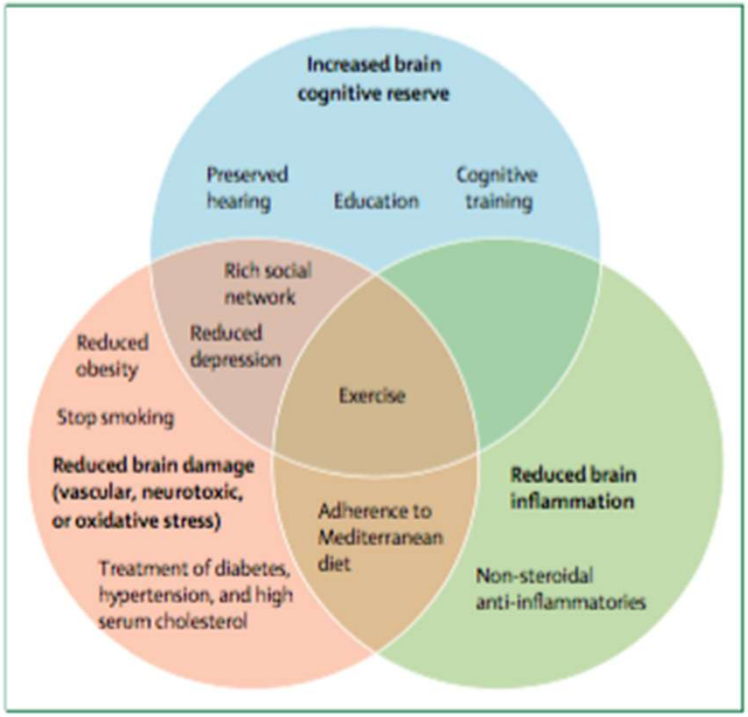
	Relative risk for dementia (95% CI)	Prevalence	Communality	PAF	Weighted PAF*
Early life (age <18 years)					
Less education (none or primary school only)	1·6 (1·26–2·01)	40·0%	64·6%	19·1%	7·5%
Midlife (age 45–65 years)					
Hypertension	1·6 (1·16–2·24)	8·9%	57·3%	5·1%	2·0%
Obesity	1·6 (1·34–1·92)	3·4%	60·4%	2·0%	0·8%
Hearing loss	1·9 (1·38–2·73)	31·7%	46·1%	23·0%	9·1%
Later life (age >65 years)					
Smoking	1·6 (1·15–2·20)	27·4%	51·1%	13·9%	5·5%
Depression	1·9 (1·55–2·33)	13·2%	58·6%	10·1%	4·0%
Physical inactivity	1·4 (1·16–1·67)	17·7%	26·6%	6·5%	2·6%
Social isolation	1·6 (1·32–1·85)	11·0%	45·9%	5·9%	2·3%
Diabetes	1·5 (1·33–1·79)	6·4%	70·3%	3·2%	1·2%

Data are relative risk (95% CI) or %. Total weighted PAF adjusted for communality=35·0%. PAF=population attributable fraction. *Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality.

Table 1: **Potentially modifiable risk factors for dementia**

Brain mechanisms preventitive strateg

http://dx.doi.org/10.1016/ S0140-6736(17)31363-6



INTERVENTIONS

For Dementia prevention in normal ageing and MCI

Medications

- Antihypertensives
  - Beneficial, with meta-analysis HR 0.13 reduction in dementia risk if SBP <150mmHg.
  - Trials in >80yo age group
  - Beneficial: healthy- MCI-Dementia

- NSAIDs
  - No benefit in MCI
  - Observational evidence- may reduce dementia
  - RCTs don’t support this, so no clear evidence of benefit

Medications cont

- Pioglitazone/rosiglitazone
  - 24week RCT: no reduction in dementia incidence
  - Biological plausibility, so current trials
- HRT
- Gingko Biloba
  - 240mg daily over 6 yrs no benefit in MCI or healthy cognition
  - Recent new trials in combination with other anti-ox eg curcumin/Gingko/

Medications

- Statins
  - No reduction in incident dementia in RCTs
  - No worsening of cognitive function in long term observational studies
- Vitamins
  - Vitamin E no benefit, possible harm
  - B grp (B12, B6 and folate) no benefit in RCT
  - Vitamin D studies currently underway

Medications in MCI

- Targeted to people with Aβ positive PET scans
  - Aducanumab reduces amyloid, ongoing f/u
- Cholinesterase inhibitors
  - No benefits in primary outcomes in RCTs
  - Increased mortality
- Fish oil
  - In Dementia no strong evidence, possibly functional benefits
  - In MCI generally no major benefit, though some studies show stabilisation/improvement. May be more targetted approach
- Souvenaid
  - No differences, in RCTs and meta-analysis

Cochrane Database Syst Rev. 2016 Apr 11;4:CD009002. doi: 10.1002/14651858.CD009002.pub3.

antioxidants

- Omega 3, 6 and Vit D3
- Recent experimental studies-
  - Alteration in innate immunity
  - Activation of macrophages/monocytes
  - Reduced deposition of Abeta
  - Stabilisation of cog decline
- Needs RCT in MCI/ early AD

FASEB J. 2017 Aug;31(8):3229-3239. doi: 10.1096/fj.201700065R. Epub 2017 Apr 18.

Resveretrol

- Ageing is major driver of AD pathology
- Calorie restriction prolongs life
- Depends on SIRT-1 ptw
- Resveretrol is a potent agonist of this pathway
  - Mimicking the positive effects of calorie restriction
  - Studies indicate effects on brain tissue
  - Reduces cognitve decline in animal models

Neurology oct 2015 20;85(16) p1381

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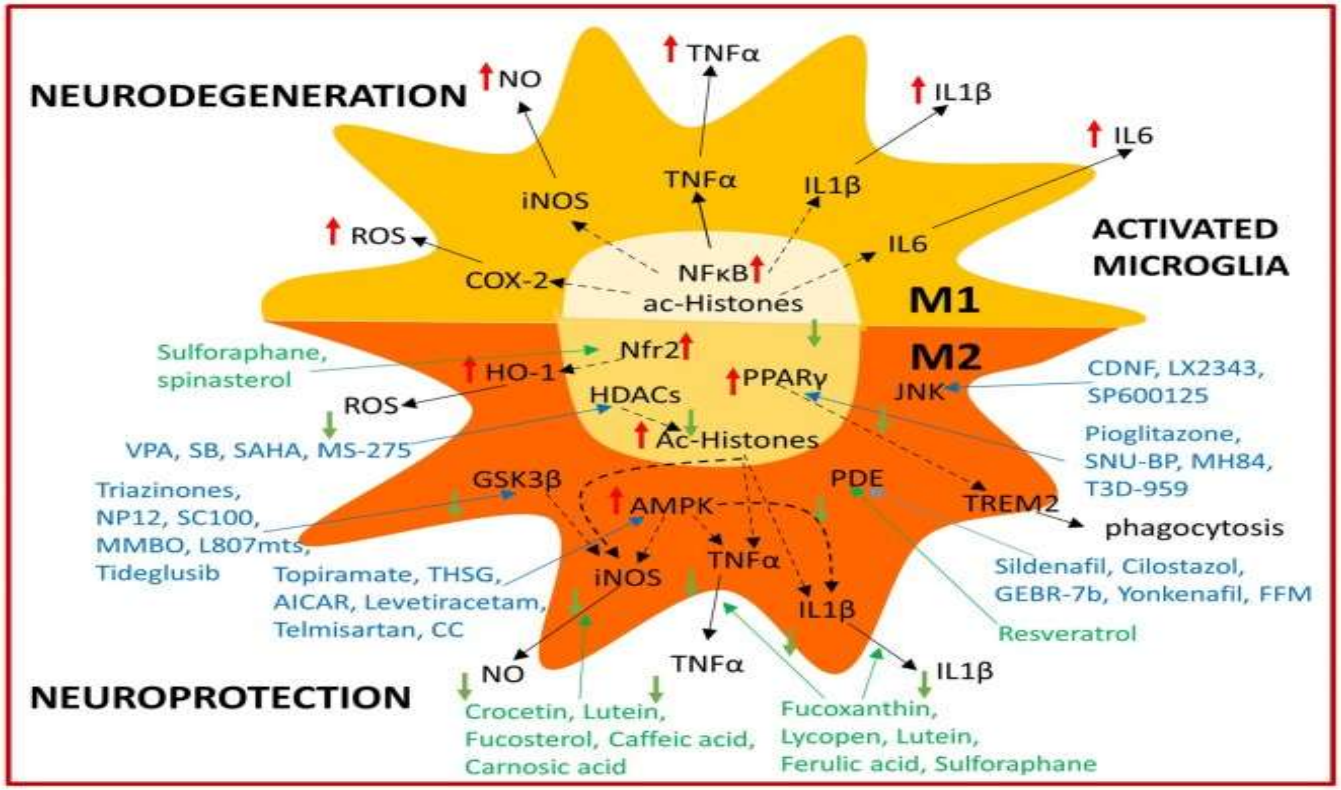

Mediterranean Diet

- RCT- 3 arms 447 participants
  - 67yo no cognitive impairment
  - 1 control, 2 intervention diets
  - f/u over 4 yrs
  - Improved cognition in intervention
- No dementia, but a lot of drop outs mainly in control group.

Cognitive stimulation

- Observational studies
  - RRR 0.33 801 older adults
  - 29279 people in 22 studies, f/u 7.1y
  - OR 0.54 (CI 0.49-0.59)
- RCTs
  - 2802 people, 10 grp sessions, with improvements
  - 10y f/u
  - Multicomponent interventions best
  - Systematic rv 4/6 studies benefit in MCI

Exercise

- Mixed results, but overall positive
- Some domains better
  - Attention, executive, speed of processing
- MCI- aerobic exercise improves memory
  - Resistance training RCT improved memory at 6months
- Mechanisms
  1. Effects on vascular risk factors
  2. Direct effect on brain eg imporved cerebral blood flow, BDNF, neurogenesis
  3. There may be individual responses to exercise neuroplasticity

Social engagement

- Longitudinal observational studies
  - Delay/prevent incident dementia
- Meta-analysis- RR1.41 ↑
- Isolation common in dementia
- RCTs:
  - Mixed results when focused only on one intervention

Multicomponent strategies

- FINGER Study
  - 600 people >60yo, diet, exercise, cog training and Vascular RF management.
  - 300h over 2 years. Improvement in cognition (small) but high risk population.
- PreDIVA study
  - 3526 people aged 70-78, 6 y f/u
  - Lifestyle and RF modification
  - No signif difference HR 0.92. Subgrp- those who hypertensive
- MAPT trial
  - 1525people >75, lifestyle and O3FAs
  - Subgrp benfit of higher risk grp

summary

- Dementia is a public health issue
- Potentially modifiable factors account for 35% of risk
- Improving understanding of mechanisms around risk and dementia
- Aggressive treatment of mid life RF will reduce dementia incidence
- Lifestyle modifications have benefits in 1° prevention and in delaying progression in MCI.

Role of microglia in neuronal life and death

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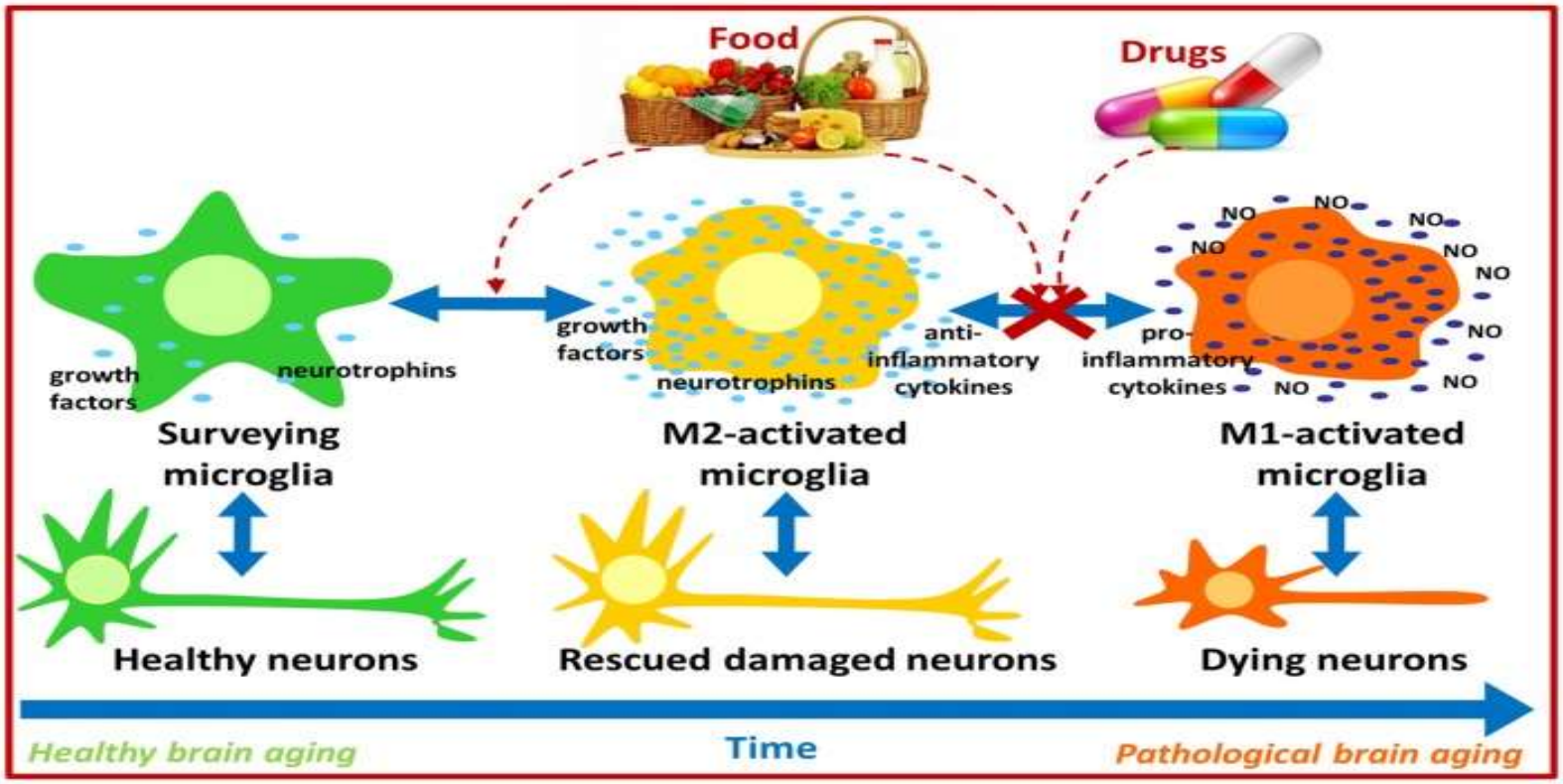
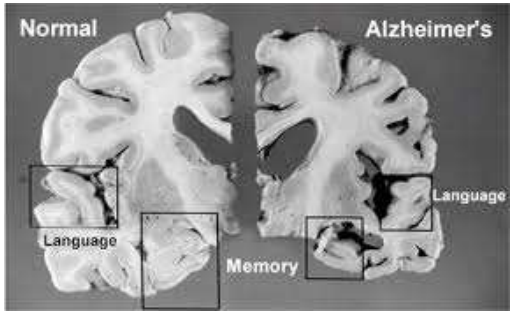
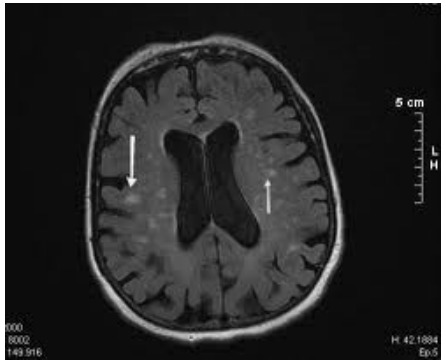
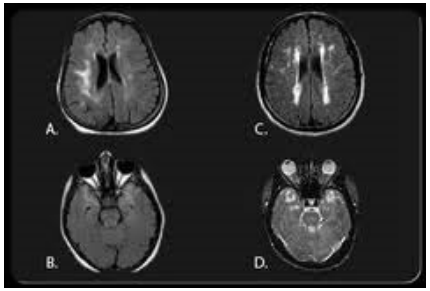
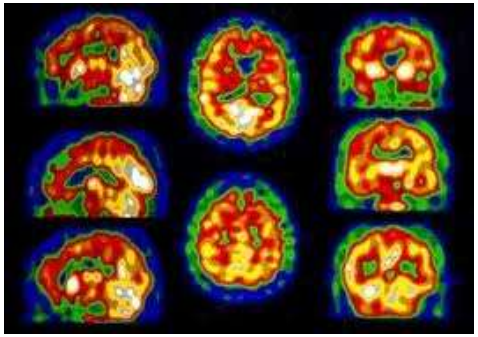


Different dementias









Established dementia

- No proven disease modifiying drugs currently
- Multicomponent interventions
  - Vary through course
- Drug therapy:
  - Cholinesterase inhibitors, Memantine
- Exercise, social activity, structred cognitive activity
- Behavioural and psychological symptoms
  - Multicomponent interventions
  - medications

Trial update

Clinicaltrials.gov

Trials in Australia for AD

- Repetitve TMS (NCT02908815)
  - Sham v 2 v 4 weeks treatment
  - Cognitive endpoints over 5-27weeks
- Deferiprone to Delay Dementia (The 3D Study)
  - Iron chelation v placebo, phase 2 trial
  - Cognitive endpoints over 12months
- CT1812 (NCT02907567)
  - Mild to mod AD
  - Phase 1 trial safety and tolerability

Trials in Australia

- ANAVEX2-73 (NCT02244541)
  - Phase 2 dose finding study
  - Cognitive outcomes after 12months
- Bapineuzumab
  - Terminated in AD- no benefit
  - Subset study in MCI
- Solanezumab
  - No benefit

- Azeliragon (NCT02080364)
  - Phase 3 mild AD, 18months f/u v placebo
  - Cognitive endpoints
- Lanabecestat in early AD- MCI (NCT02245737)
  - 104 week f/u placebo v drug
  - Cognitive endpoints, biomarker substudy
- ALZT-OP-1a/b (NCT02547818)
  - Cromoglycate and NSAID v placebo
  - 72 weeks

Trials in Australia

- Elenbecestat (NCT02956486)
  - 24months v placebo, phase 2-3
  - Biomarker study with cognitive endpoints
- ABBV-8E12 (NCT02880956)
  - Early AD/MCI, 96 week f/u
  - IV infusion, phase 2
- Pioglitazone (NCT02284906)
  - MCI f/u 7yrs pio v placebo
  - Cognitive endpoints

Trials in Australia

- LY3202626 (NCT02791191)
  - Oral 52 week v placebo
  - Imaging end points, phase 2 trial
- JNJ-54861911
  - positive amyloid scan- no dementia
  - 54 month f/u, phase 2 and 3
- Suvorexant
  - Phase 3 placebo v control
  - Measures of insomnia

Trials in Australia

- Xanamem (NCT02727699)
  - Hydroxysteroid dehyrogenase type 1 inh
  - Reduces intra-cerebral cortisol
  - Phase 2, 20 week f/u cognitive outcomes

Thank you