Preventing Dementia and Enhancing Brain Health

Henry Brodaty

UNSW SYDNEY | Australia's Global University

DCRC Dementia Collaborative Research Centres

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Ronald and Nancy Reagan, USA

"I have recently been told that I am one of the Americans who will be afflicted with Alzheimer's disease. ... I will continue to share life's journey with my beloved Nancy and my family. I plan to enjoy the great outdoors and stay in touch with my friends and supporters"

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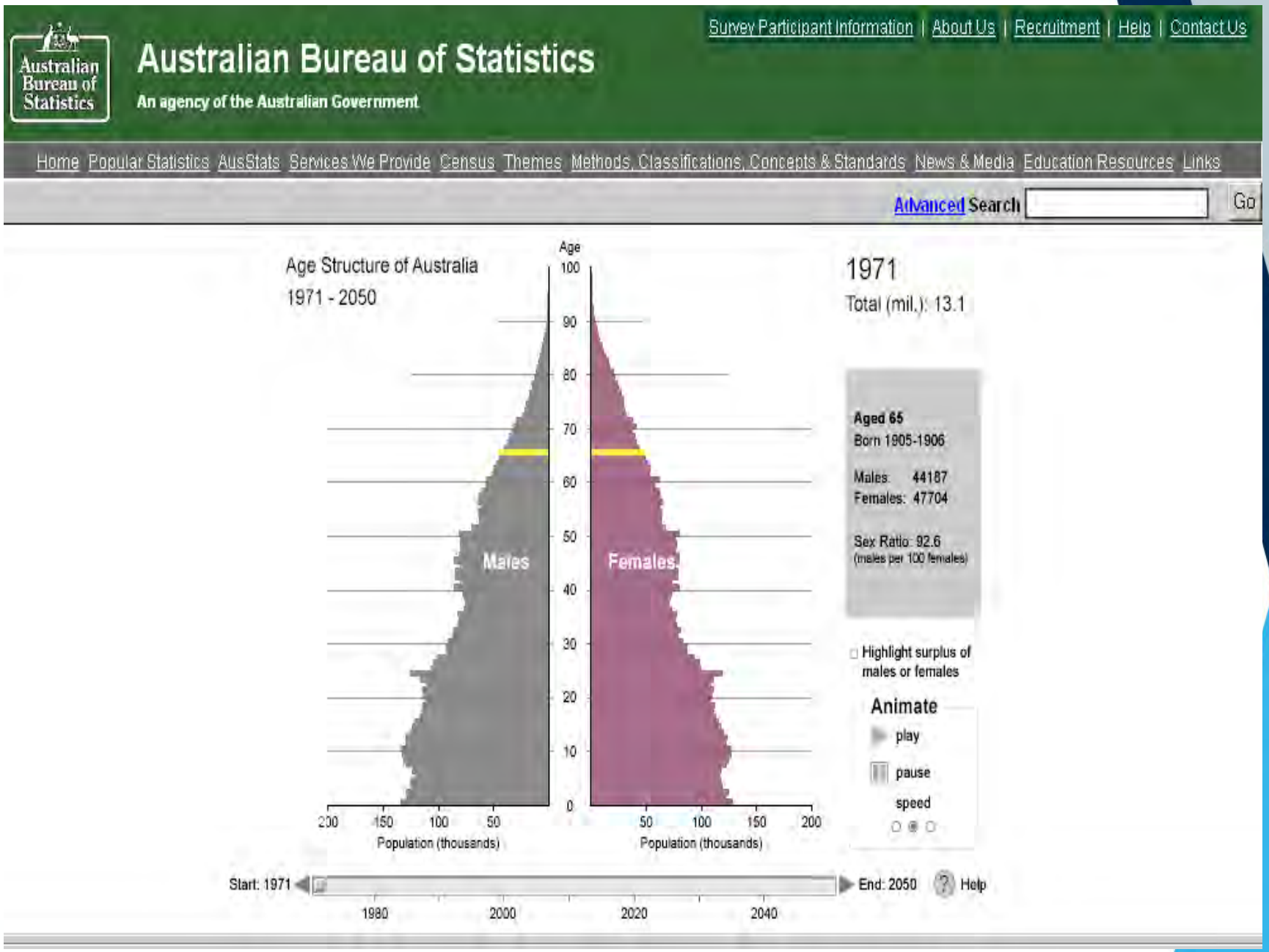

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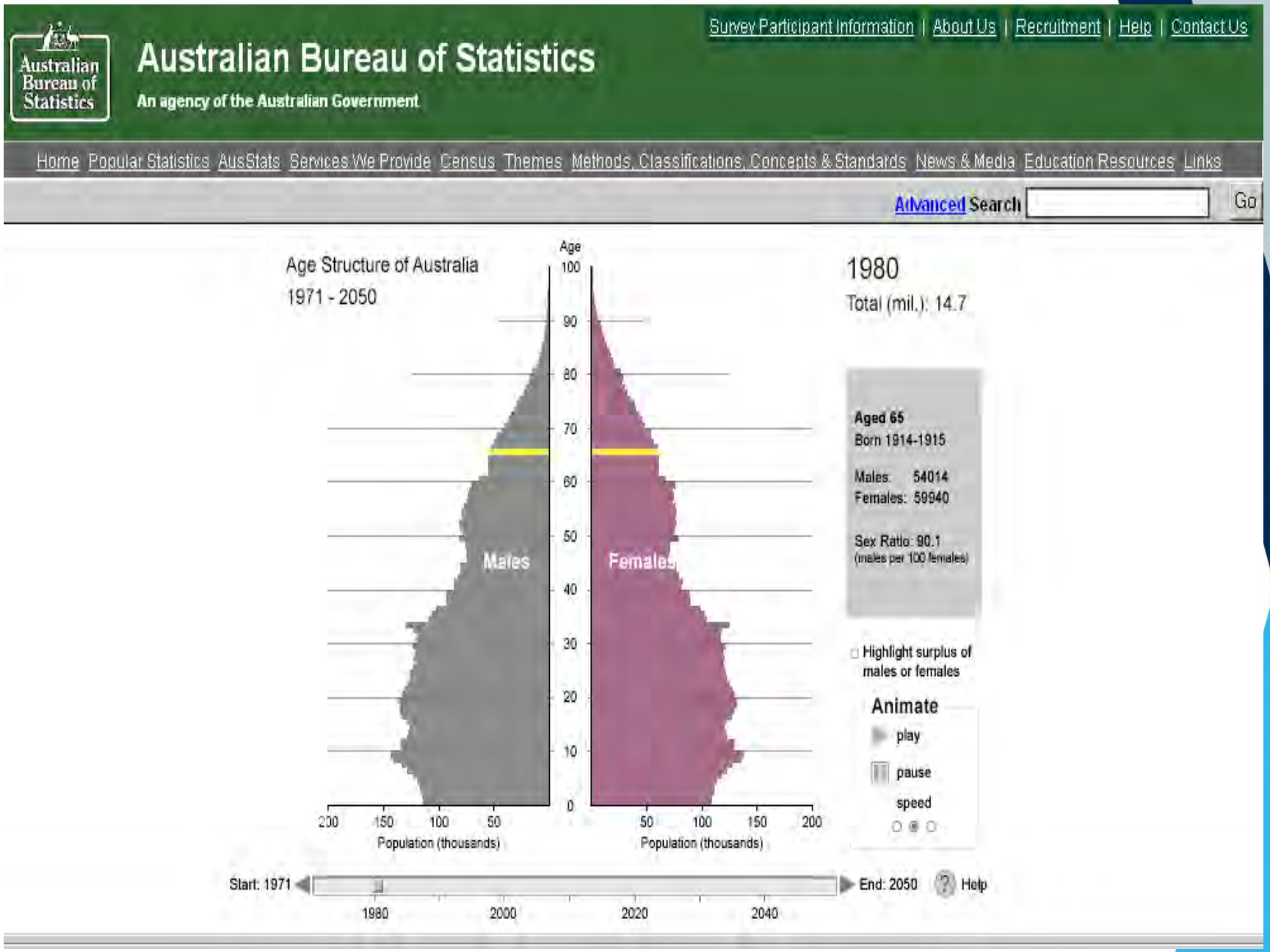

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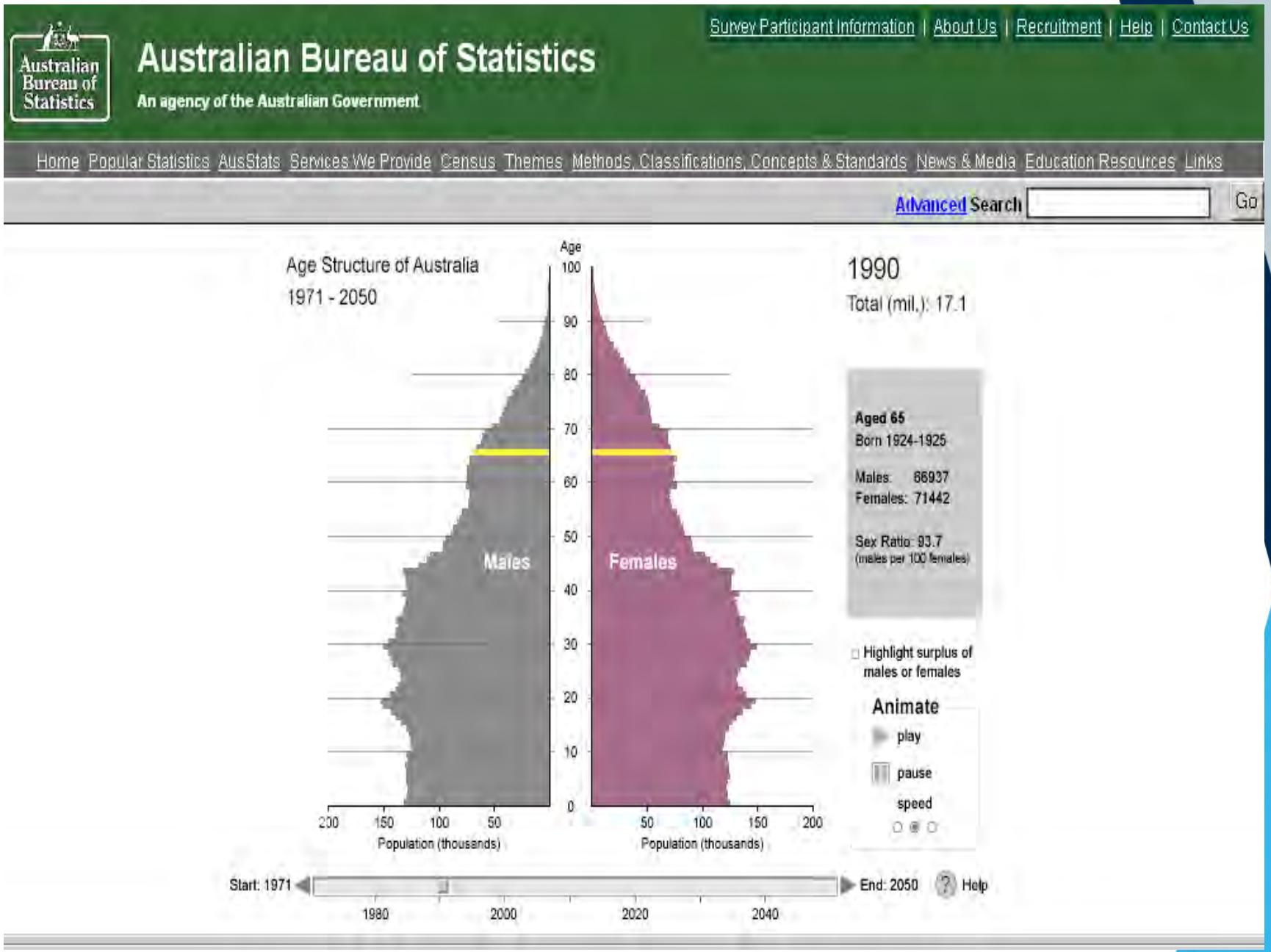

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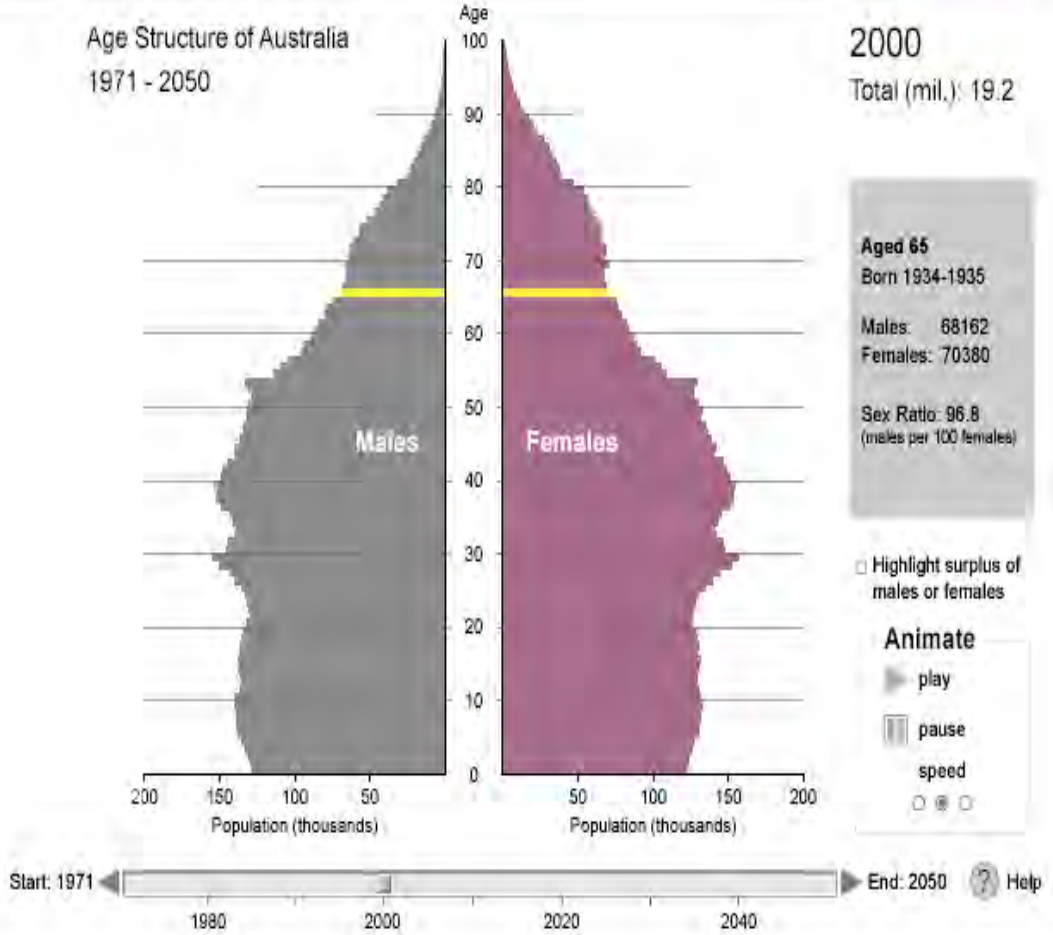

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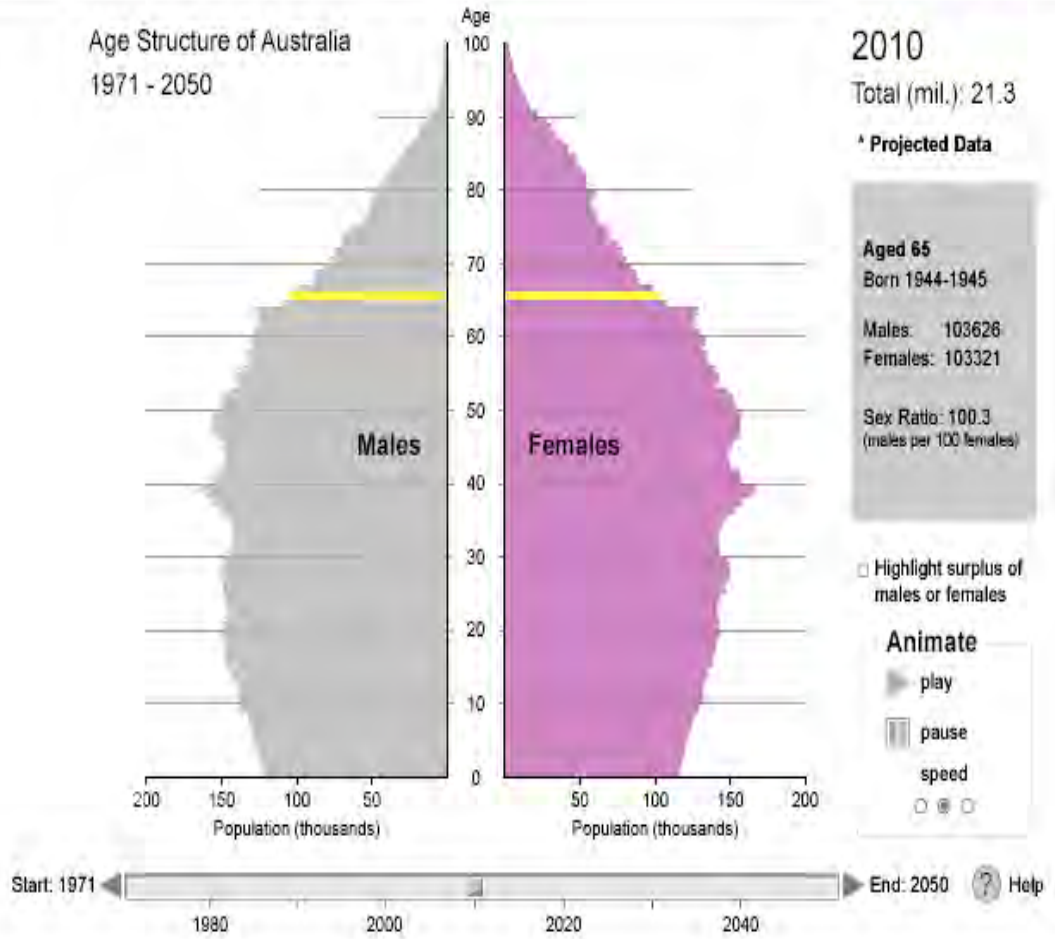

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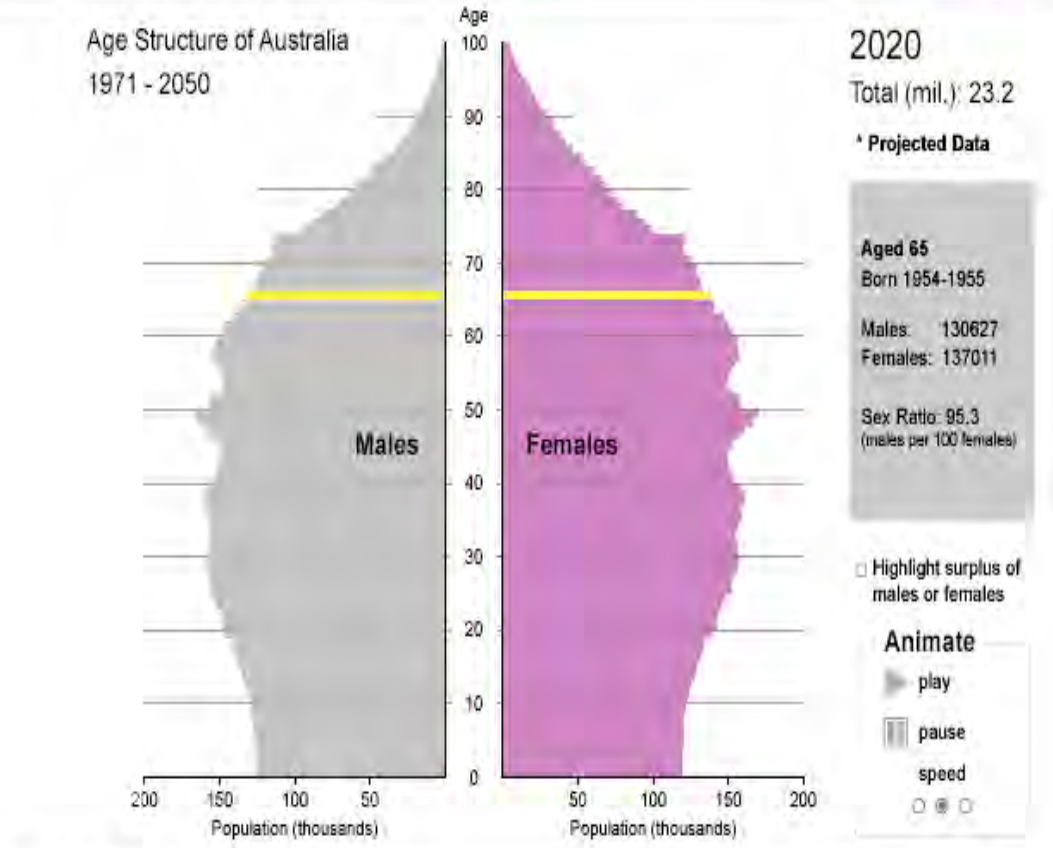

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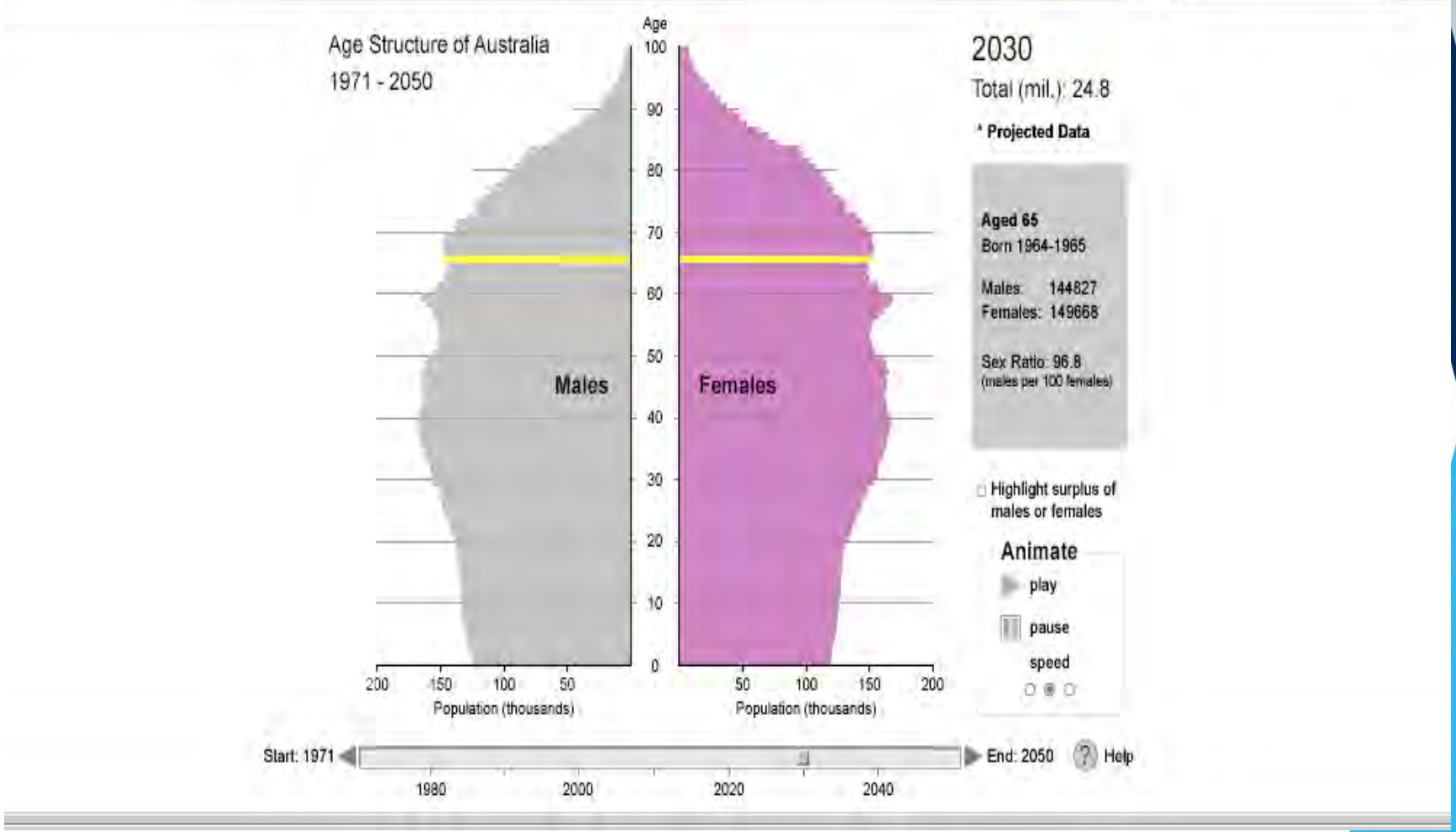

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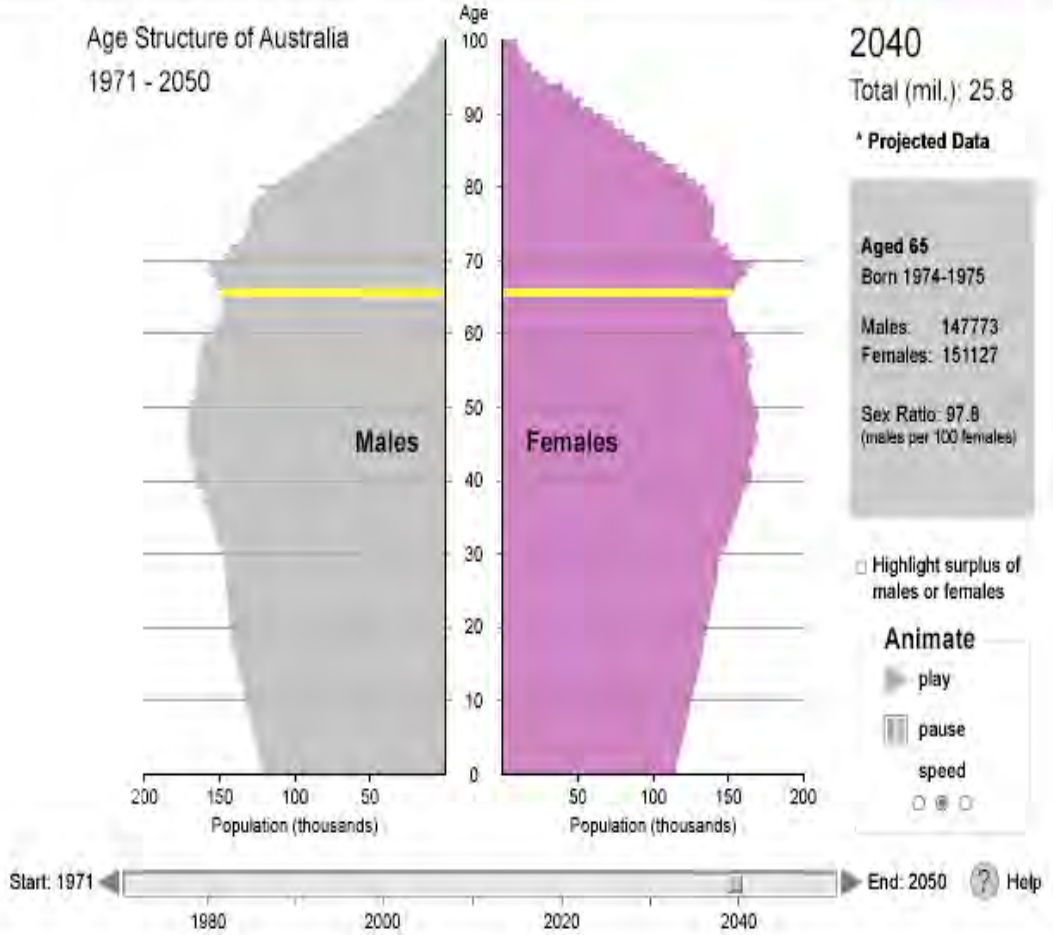

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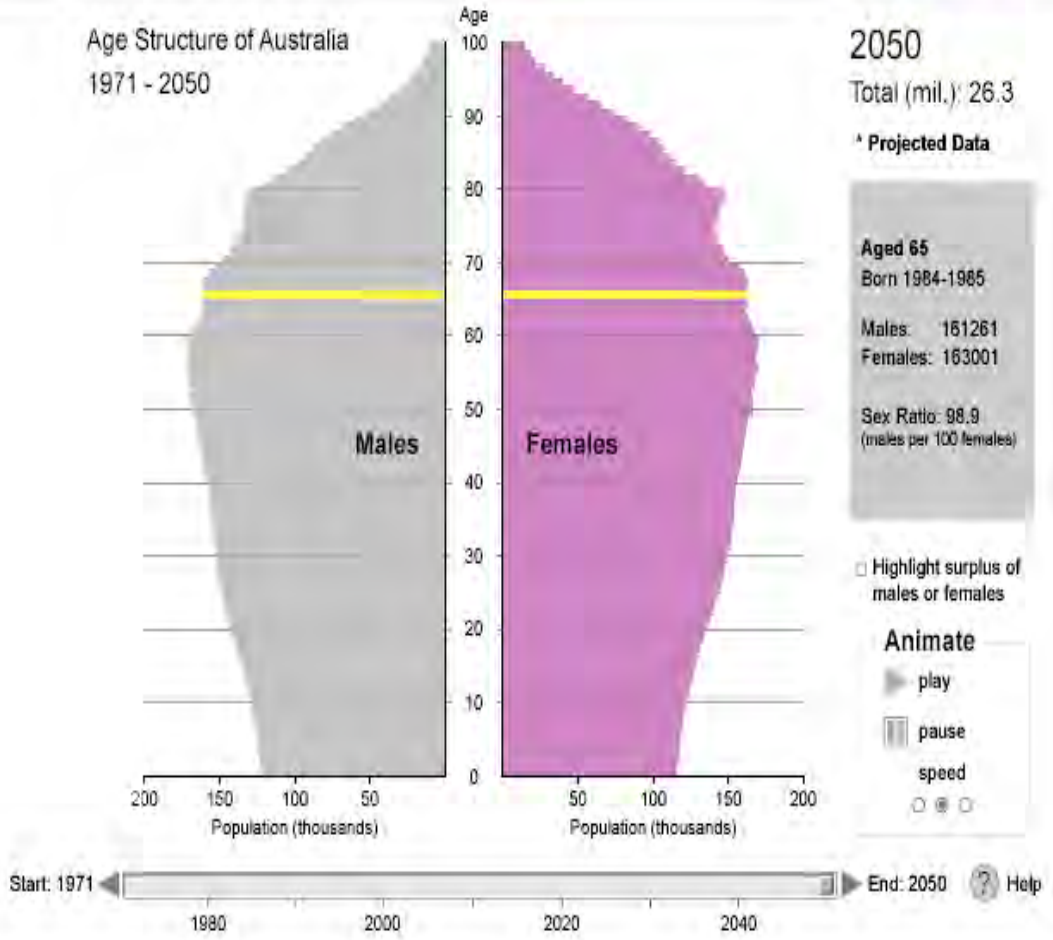

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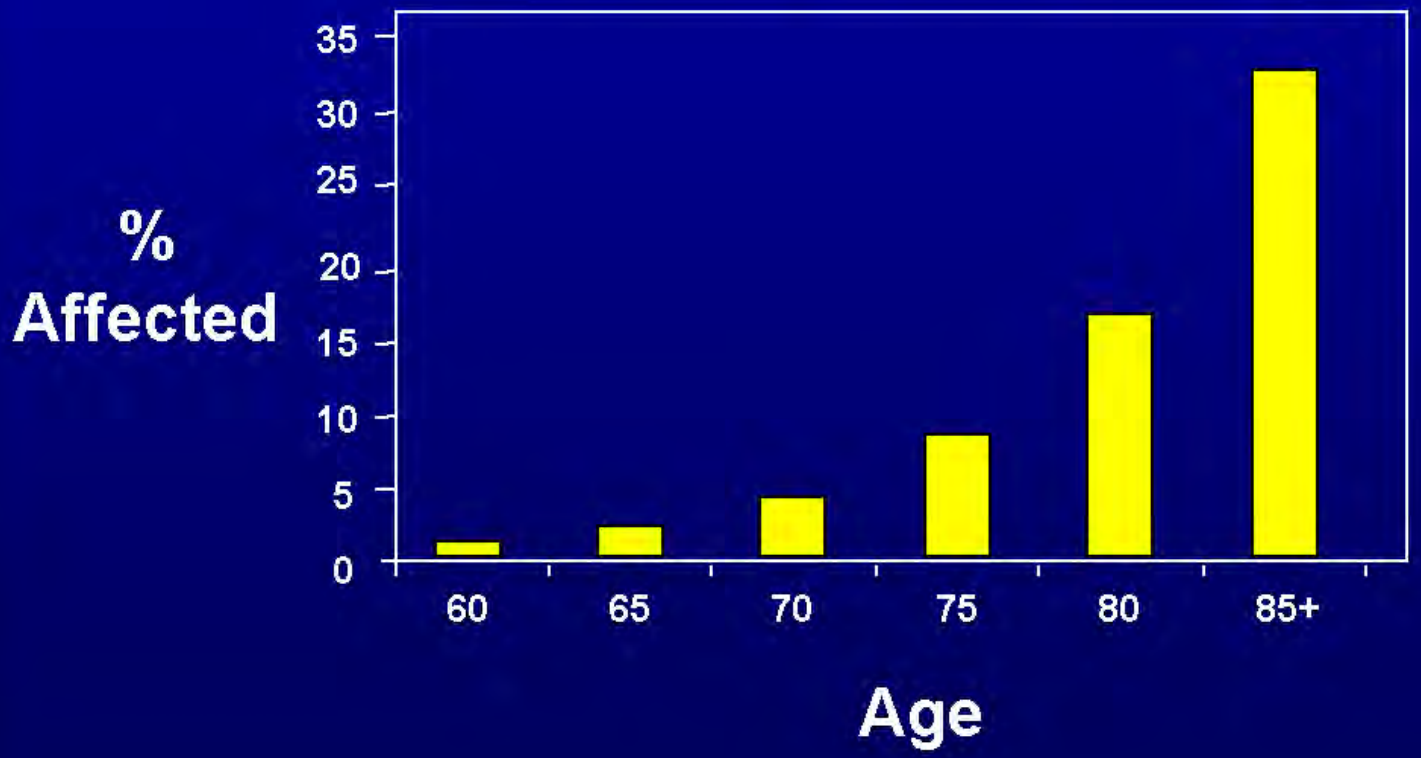
Dementia Doubles in Frequency Every 5 Years After Age 60



Evans et al. *JAMA*. 1989.
Jorm et al. *Acta Psychiatr Scand*. 1987.

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Can we prevent dementia?

- The adult brain weighs about 1.3 kg
- Dementia shrinks it to 1/2 its usual size

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What are we aiming to prevent: dementia, Alzheimer's disease, vascular dementia, mixed dementia?

- With ↑age, % of pure type of dementia decreases
- In older people, mixed dementia is more common than Alzheimer's disease
- 80%+ of older people with dementia have cerebrovascular disease at post mortem
- Most effort has been on preventing/delaying Alzheimer's disease
- Vascular disease of the brain, strokes may be more preventable

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Elimination vs Postponement

- Disease elimination
  - eg smallpox vaccination
  - best prospect is AD vaccine
- Disease postponement[1]: delay AD onset by…
  - 2 years, ↓ prevalence by 20%
  - 5 years, ↓ prevalence by 50%

[1]Brookmeyer et al. (1998)

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Life Course Approach: childhood

- Genetic determinants
- Environmental determinants
  - Foetal maldevelopment
  - Low birth weight *for gestational age*
  - Low education
  - Low parental education & occupation
  - Low socio-economic status
  - Dietary history
  - Loss of parent before 11yo

} Reduced cognitive reserve

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Whalley L et al, Lancet Neurology, 2006;5:87-96; Whalley L et al, IJGP, 28:75-81

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Is early life the most important target?

- 70% of world dementia in developing countries where there are high rates of:
  - Low foetal birth weight for gestational age
  - Poor education
  - Poor socio-economic environment

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YOUR BRAIN MATTERS

A GUIDE TO HEALTHY HEARTS & MINDS

- Look after your heart
- Be physically active
- Mentally challenge your brain
- Follow a healthy diet
- Enjoy social activity

yourbrainmatters.org.au

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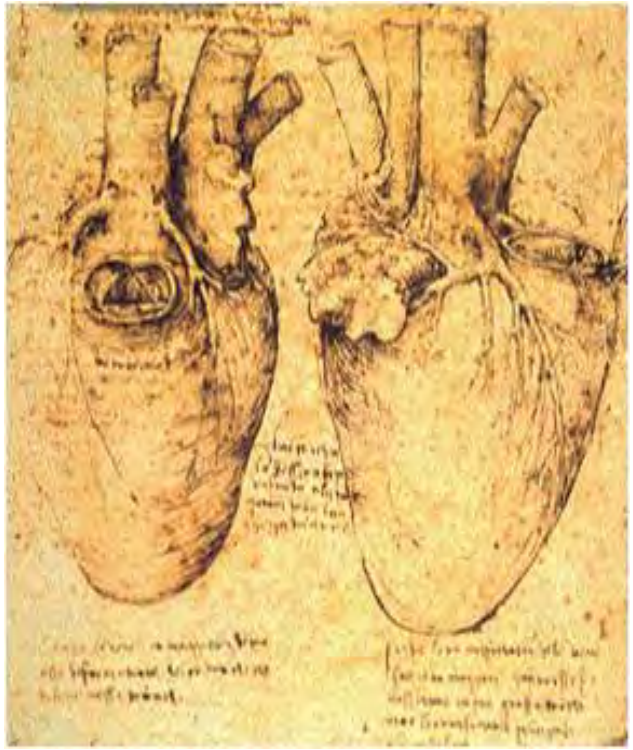
Cardiovascular Factors



The human heart
Leonardo Da Vinci

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Blood Pressure & Dementia

- Mid-life hypertension associated with late-life dementia
- Treating blood pressure decreases risk in some studies
- Each year of treatment decreases risk

Caveats

- Can harm if lower BP too much in older old

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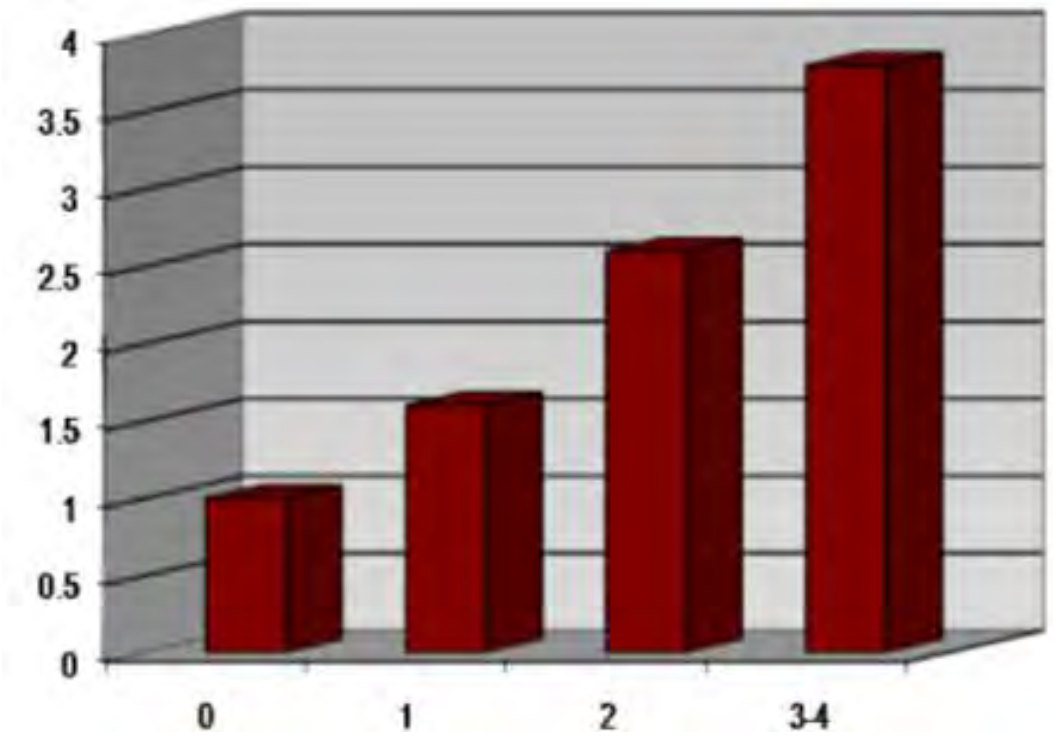
Dosage Effect

The more vascular risk factors the greater AD/ dementia risk

- ***Hypertension***
- ***Smoking***
- ***Hypercholesterolemia***
- ***Obesity***
- ***Diabetes***
- ***Physical inactivity***

Luchsinger et al 2005



Number of risk factors

Slide adapted from Michael Valenzuela

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SPRINT- MIND Trial

- Does treating high blood pressure to target < 120 mm Hg systolic better than < 140 mm
- 9361 hypertensive older adults with high CV risk but no diabetes, dementia or stroke
- At 1 year, mean sBP 121 vs 134
- Less mild cognitive impairment in intensive BP treated group and trend for less dementia
- Also less increase over 4 years in white matter lesions

Statins to prevent AD

- Statins neither prevent nor increase risk of cognitive impairment or dementia[1]
- Benefits of statins may vary by type of statin, sex, race[2]

[1] McGuiness B et al, 2016; CD003160 (1) Cochrane Database of Systematic Reviews

[2] Zissimopoulos J et al, JAMA Dec 2016

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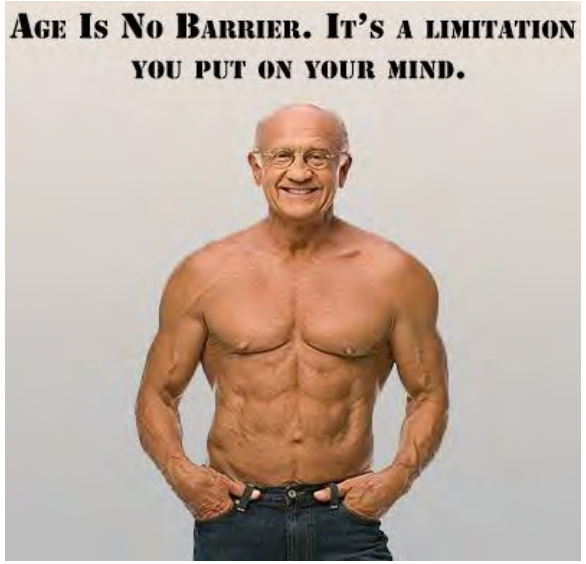
Physical activity = Protective

- Several studies show physical activity protective against cognitive decline, dementia, Alzheimer's, vascular dementia
- More is better – puffed, weights
- At least three times per week
- At least 150 minutes per week
  Check with your doctor



[1]Jedrziewski et al (2007). Alz Dem; 3:98-108; [2] Lautenschlager et al (2008) JAMA; 300(9):1027-1037; [3]Ravaglia et al (2007) Neurology; [4]Larson et al (2006) Ann Intern Med; 144:73-81; [5]Laurin et al, Arch Neurol 2001;58:498-504; [6]Middelton et al, PLos ONE 2008;3(9):e3124

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Can aerobic exercise protect against dementia?

- Preserves cognition and slows cognitive decline
- Decreased incident dementia
- 8/11 Randomised Control Trials in healthy older persons: cognition & fitness improved
- Biomarkers improved, e.g. brain volume
- Animal studies – growth factors improved, brain derived neurotrophic factor improved, more new nerve cells, less inflammation
- Less Alzheimer's disease pathology

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Physical activity

- Physical activity benefits older adults to prevent dementia: Never too late to start; never too early
- Moderate intensity (brisk walking) 30 min 5d/wk
- Evidence for specific exercise not clear; more than one type and more exercise may be better
- Resistance training better in SMART Trial[2]
- Combine physical, social and mental activity better?
  - Eg dancing

Denkinger et al. *Z Gerontol Geriat 2012*; 45:11–16 DOI 10.1007/s00391-011-0262-6
Fiatarone Singh MA et al *JAMDA* 2014;15:873-80

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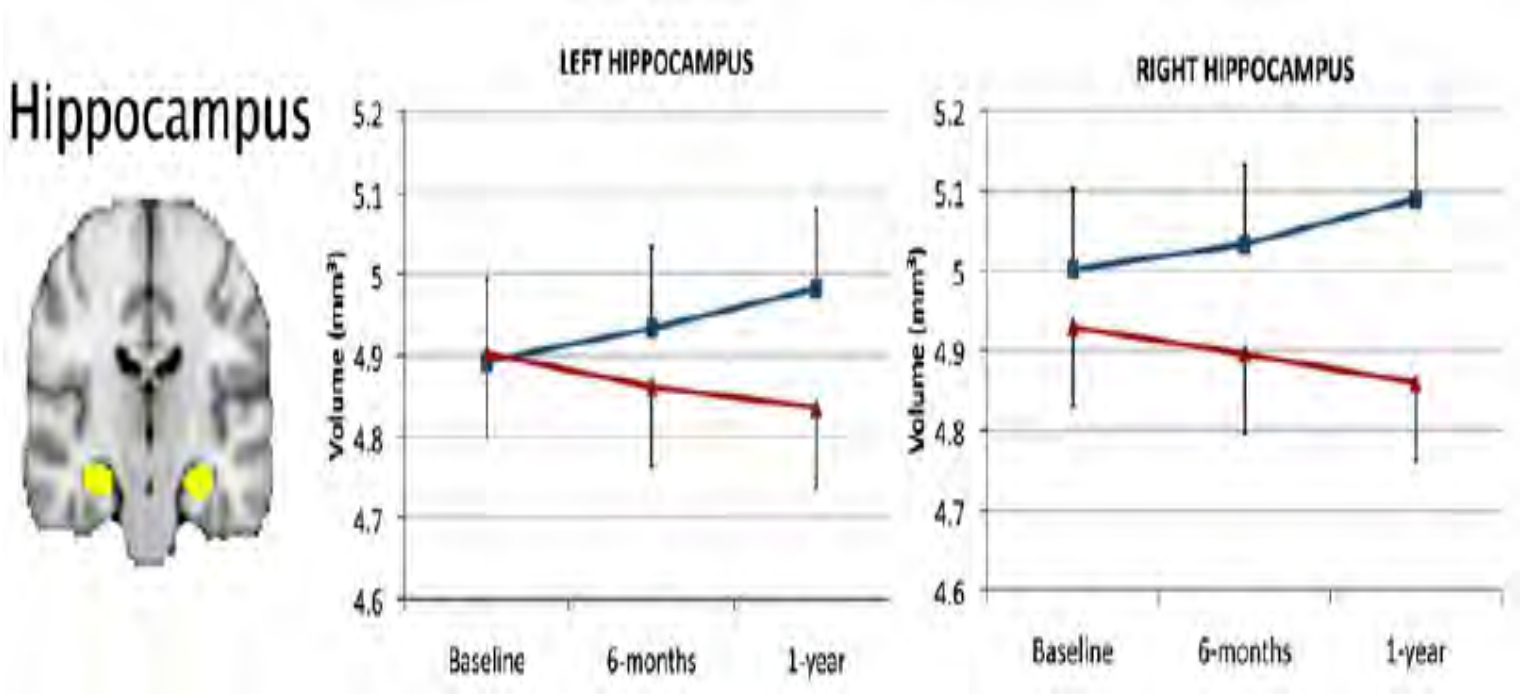
The power of physical activity



Erickson et al., 2011

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Physical activity benefits

- Improved fitness
- Improved physical health - ↓ heart disease, Hi BP, diabetes, some types of cancer, osteoporosis, sarcopenia
- Reduced morbidity & mortality
- Improved mental health
- Improved confidence, quality of life

Cognitive interventions healthy older adults and people with Mild Cognitive Impairment

- 20 RCTs with healthy adults
  - Memory improvements in 17/20
- 6 RCTs with MCI
  - Memory improvements in 4/6
- Unclear whether these improvements generalise to everyday activities
- Review of cog. training or rehabilitation in dementia
  - 11 RCTs, no benefit

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Obesity in Mid-Life

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Mid-Life Obesity

- Compared to normal weight, midlife obesity increases risk of dementia later in life
  - BMI 25-30: 34% increased risk
  - BMI > 30: 91% increased risk
- Obesity paradox: In late life being overweight is not a risk factor, may be protective

Mind your diet

- Mediterranean diet
- Antioxidants

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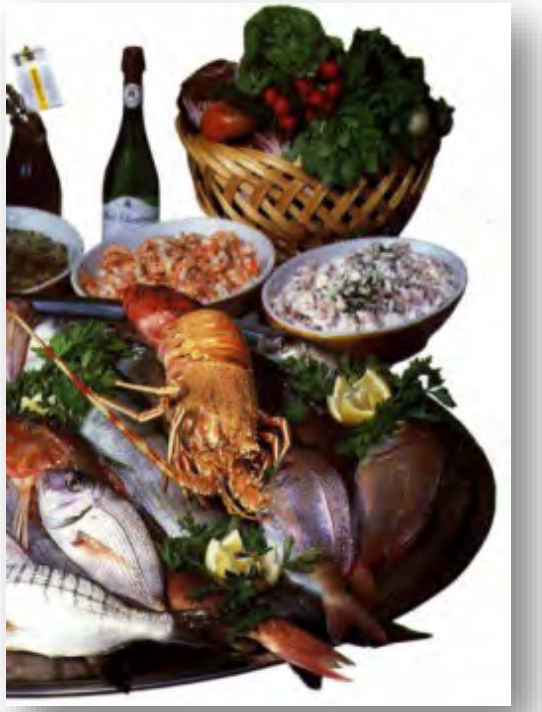
What is Mediterranean diet?

- Abundant plant foods
- Fresh fruit as typical daily dessert
- Olive oil as principal source of fat
- Dairy products (cheese, yogurt)
- Fish and poultry - low to moderate
- 0- 4 eggs week
- Red meat - low amounts
- Wine - low to moderate amounts
- Total fat = 25% to 35% of calories
- Saturated fat ≤ 8% of calories



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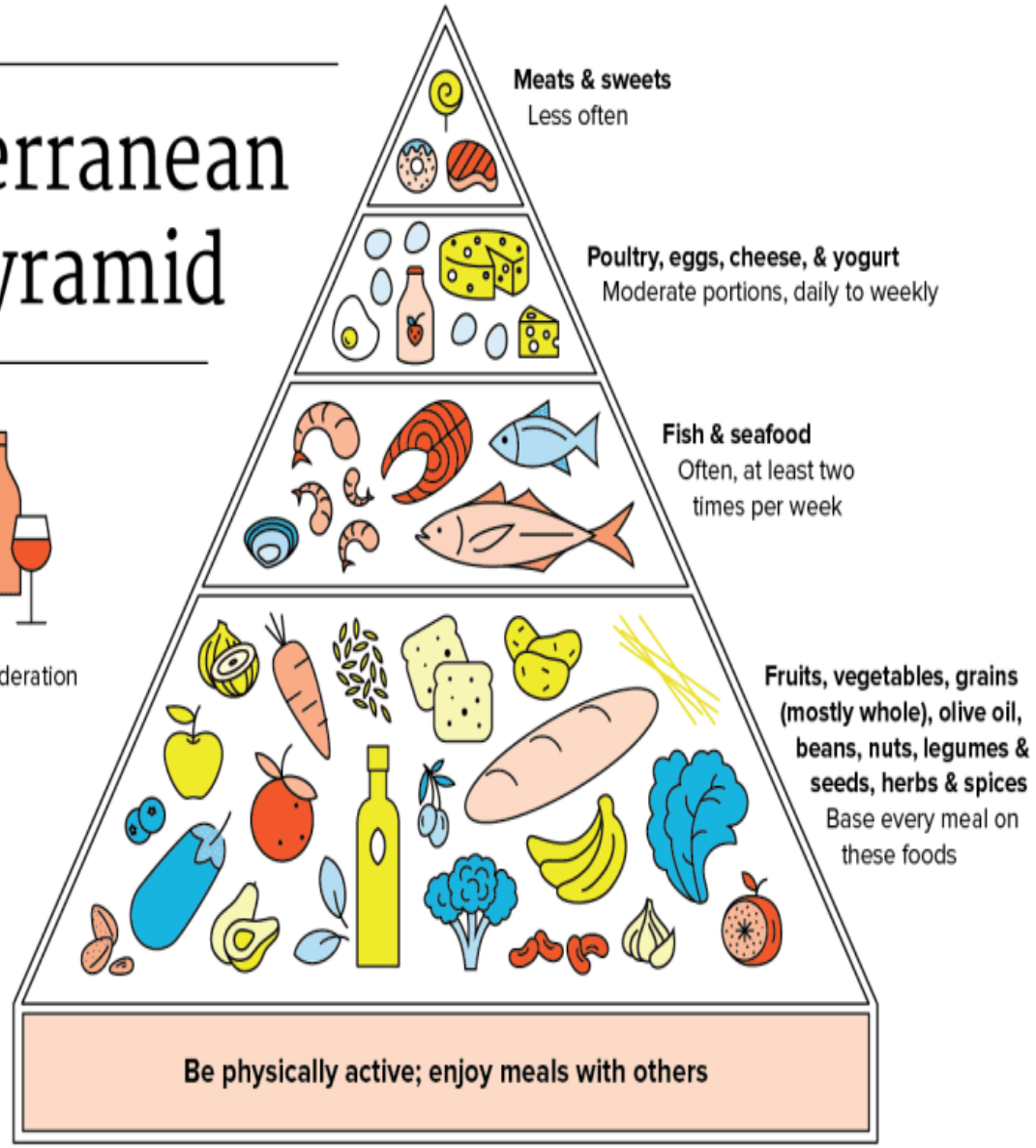
Mediterranean Diet Pyramid



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Western diet v Eastern diet

Centenarian Hotspots Blue Zones

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Blue Zone: Okinawa, Japan

- General female life expectancy = 87yrs
- Increase in centenarians:
  - 30 (1975) → ↑ 1000 (2016)
- ~35% function independently
- Factors influencing longevity:
  - Diet?
  - Genetics?
  - Physical activity?

Willcox et al. (2016), Mechanisms of Ageing & Development

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Okinawa: Reasons for Longevity

- A lean diet with fewer calories:
    - Vegetables
    - Tofu
    - Miso soup
    - A little fish or meat
- Confucian-inspired adage:
    - "hara hachi bu” = until your stomach is 80% full

National Geographic, Nov 2005

Nutrition / Supplements

- Fish√ ω3 ?
- Vitamin D ?
- Caffeine ?
- Vitamin E ?
- Vitamin C x

Food sources better than supplements

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B Vits and homocysteine

- OPTIMA: Folate 0.8mg + Vit B_{12} 0.5mg + B_6 20mg
  - Reduce brain atrophy and improve cognition
  - Mainly in people with high homocysteine
- Two systematic reviews and one trial no benefit from homocysteine lowering Rx

- Smith AD et al, PLoS ONE, 2010; Douaud et al. PNAS 2013;110:9523-28
- Ford AH, Almeida OP Systematic review 19 RCTs *J Alz Dis.* 2012;29:133-49 doi: 10.3233/JAD-2012-111739
- Clarke R et al Am J Clin Nutr 2014;100:657–66
- van der Zwaluw, Neurology;2014:83:1–9

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Vit D, NSAIDs, fish, curcumin

- Vit D – low levels of Vit D are common and associated with development of dementia
  - No evidence that taking Vit D lowers risk
- Anti-inflammatories – mixed epidem. evidence
- Fish oil – some evidence, natural source ie fish (epidemiological)
- Curcumin – some evidence (laboratory)

Smoking and AD

- Current smoking
  - increase risk for AD
- Previous smoking
  - Risk not significantly increased

Anstey K. Am J Epidem 2008

Alcohol

- Weak evidence benefit of moderate alcohol
  - i.e. abstinent → higher risk, j-shaped curve
- What is *moderate*?
- Not all studies confirm
- Heavy alcohol is risk factor
- Which alcohol – (red) wine?
  - Evidence not strong
- Alcohol linked to higher rates of cancer

Natural therapies

- Ginkgo biloba X
- Turmeric, curcumin ?
- DHA, omega 3 ??
- Fo-ti root
- Soy isoflavone
- Vitamin E, Selenium X
- Saffron
- Brahmi
- Huperzine A

Ginkgo leaves

Member of ginger family

Unproven but popular on net

- Coconut oil
- Grain Brain
- Ketogenic diet
- Many others??

Promising?

- Resveratrol, activates sirtuins
- Next generation anti-ageing compounds

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Hearing loss

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Hearing loss and incident dementia

- Lin 2011 RR 2.32 (1.32-4.07)
- Gallacher 2012 RR 2.67 (1.38-5.17)
- Deal 2016 RR 1.55 (1.10-2.19)
- Peripheral hearing loss associated with significant risk for dementia
- Follow-ups 9,12 and 17 years

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Social isolation

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Socialisation and dementia

- Less frequent social contact, less social participation, and more feelings of loneliness associated with increased risk of dementia
- 57% increase risk = comparable to late-life depression 85% and physical 82% incr^{d} risk
- Good social engagement, pooled reduction in risk 22%, (but significant publication bias)

Penninkilampi R, Casey A-N, Fiatarone-Singh M, Brodaty H. 2018

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Hormone Replacement Therapy

- **HRT – neither harmful or beneficial close to menopause**
- **Increased risk in women taking HRT from age 65yr?**

Sleep and dementia

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Sleep and dementia

- About 1-in-2 older adults have regular insomnia
- About 1-in-2 older adults have sleep-disordered breathing
- Slow wave sleep associated with amyloid-β protein clearance from brain in animal and human studies
- Sleep-disordered breathing associated with poor sleep
- Poor sleep associated with worse cognition
- Can correcting insomnia and sleep-disordered breathing prevent or delay?
- Does incipient dementia cause sleep disorders?

Environmental factors

- 30% of population attributable risk of AD cases from 7 environmental factors
- If 25% lower prevalence of these risk factors → 3 million fewer AD cases worldwide
- Highest estimated Population Attributable Risk for AD
  - Global: low education contributes ≈20%
  - USA, Europe, UK : physical inactivity contributes ≈20%

Barnes & Yaffe, 2011; Norton et al, 2014

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How much AD can be attributed to environmental factors?

- 2% diabetes mellitus (type 2)
- 2% midlife obesity*
- 5% midlife hypertension
- 10% depression
- 13% physical inactivity*
- 14% smoking
- 19% cognitive inactivity/education#

Barnes & Yaffe, 2011

Is incidence of dementia/ cognitive impairment declining?

- Review 14 studies … trends in dementia prevalence (9 studies) and incidence (5)
- Sweden, Spain, UK, Netherlands, France, USA, Japan and Nigeria.
- All (except Japan) → stable or declining prevalence and incidence of dementia
- Some effects in males; others females only
- No single risk or protective factor fully explains observed trends, but …..

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Wu YT et al Nature Neurology Reviews 2017

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Is incidence of dementia/ cognitive impairment declining?

- ….major societal changes and improvements in
  - living conditions, early childhood
  - education
  - healthcare , cardiovascular
- might have favourably influenced physical, mental and cognitive health throughout life, and
- be responsible for ↓ risk of dementia in later life

Wu YT et al Nature Neurology Reviews 2017

But…. How reliable are these findings?

- Most studies are observational or single interventions
- Reverse causality?
  - Alzheimer's disease builds up in brain over 20+ years before it becomes clinically evident
  - Could incipient dementia lead to less cognitive activity, exercise, socialisation, etc
- Can intervention studies prove that adopting these recommendations decrease cognitive decline?

Multi-component intervention studies

- FINGER
- Pre-DIVA
- MAPT
- HATICE
- Maintain Your Brain

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FINGER study

- Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
- Interventions
  - Diet
  - Cognitive training
  - Exercise – PMR and aerobic
  - Manage metabolic & vascular risk factors
  - Social activities

Ngandu et al. *The Lancet. 2015;*
http://dx.doi.org/10.1016/S0140-6736(15)60461-5

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FINGER study

- At 2 years improvement on
  - Composite Neuropsychological battery
  - Speed of information processing
  - Executive functioning
  - Complex memory (but not memory overall)
- At 5 years other benefits on health

Ngandu et al. *The Lancet. 2015;*
http://dx.doi.org/10.1016/S0140-6736(15)60461-5

PreDIVA trial

- Long-term, nurse-led vascular care in an unselected population of community dwelling older people is safe and may reduce incidence of non-Alzheimer's dementia
- Potentially clinically meaningful effects in lowering incident dementia in people with untreated hypertension adherent to intervention
- Control treatment was good

Moll van Charante EP, Lancet 2016

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Internet-based therapies: Advantages

- Home-based
- Geographically isolated individuals
- Scalable
- Relatively cheap (but not free)

Current trials:

- HATICE (Richard E_BMJ Open 2016;6(6):e010806)
- MYB (Heffernan M et al, 2019)

Internet-based therapies: Disadvantages

- Requires IT Platform development ++
- Requires Central HQ to run and monitor
- Not everyone has computer or internet access or is tech-savvy
- Not yet proven to work

Healthy aging through internet counselling in the elderly (HATICE)

- Develop an innovative, interactive internet intervention platform to optimise treatment of cardiovascular disease in the elderly
- Test this new intervention in a RCT to investigate whether new cardiovascular disease and cognitive decline can be prevented
- Trial completed, not yet published

- Richard E, http://www.hatice.eu/

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Maintain Your Brain tria

https://www.maintainyourbrain.org/

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MAINTAIN YOUR BRAIN

led by the Centre for Healthy Brain Ageing (CHeBA), is the largest clinical trial in the world targeting risk factors for Alzheimer's disease and dementia for people aged 55-77 using online tools.

I AM A MYB PARTICIPANT

ABOUT MAINTAIN YOUR BRAIN

Type here to search

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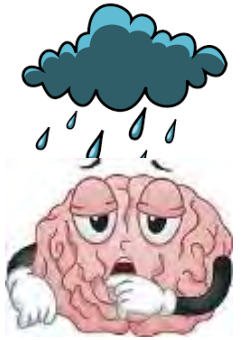
4/05/2019

RCT: Four basic modules

Physical activity

Diet & nutrition

Brain training



Depression

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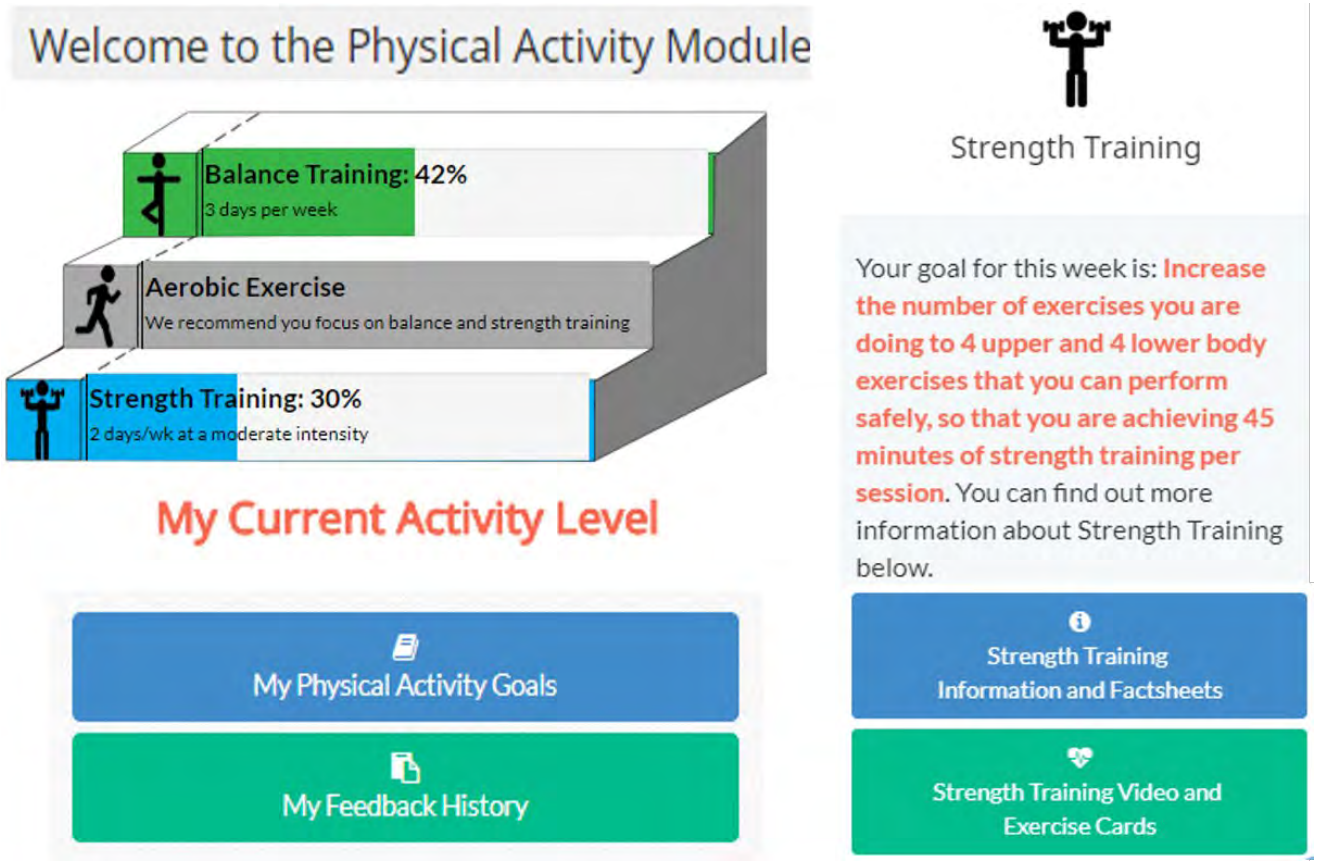
Physical Activity



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Nutrition

Welcome to the Nutrition Module

- How to piece it together
- The Mediterranean pyramid
- The Mediterranean cuisine and lifestyle
- The Mediterranean pantry and shopping list
- Sample menu plan
- Meal and snack ideas
- Recipe library
- Food allergies, intolerances and drug interactions
- Scientific literature

My Mediterranean Goals

The Mediterranean Diet

The Ideal Mediterranean Diet

Brain Training (BTS)

Graph summarising performance across all training exercises

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Peace of Mind

THIS WAY UP

Update My Details Log

Courses

You are enrolled in the following course(s):

Mixed Depression and Anxiety (Access Expires: 01/08/2018)

People with depression and anxiety experience weeks of sadness, loss of interest and energy, uncontrollable and excessive worry, and avoid situations they feel they can't cope with. This program is designed to help people who experience both depression and anxiety. It involves six lessons over an 8 week period.

Continue Course | View Resources

Registration **Course Expiry**

63 days remaining

Lesson 1 | Lesson 2 | Lesson 3 | Lesson 4 | Lesson 5 | Lesson 6

Mixed Depression and Anxiety

About anxiety and depression

In this lesson, you will be introduced to Liz and Rob who struggle with depression and anxiety. Here they both learn about their symptoms, and learn how to start tackling the physical symptoms of depression and anxiety.

This course consist of six lessons over an eight week period.

Start Lesson

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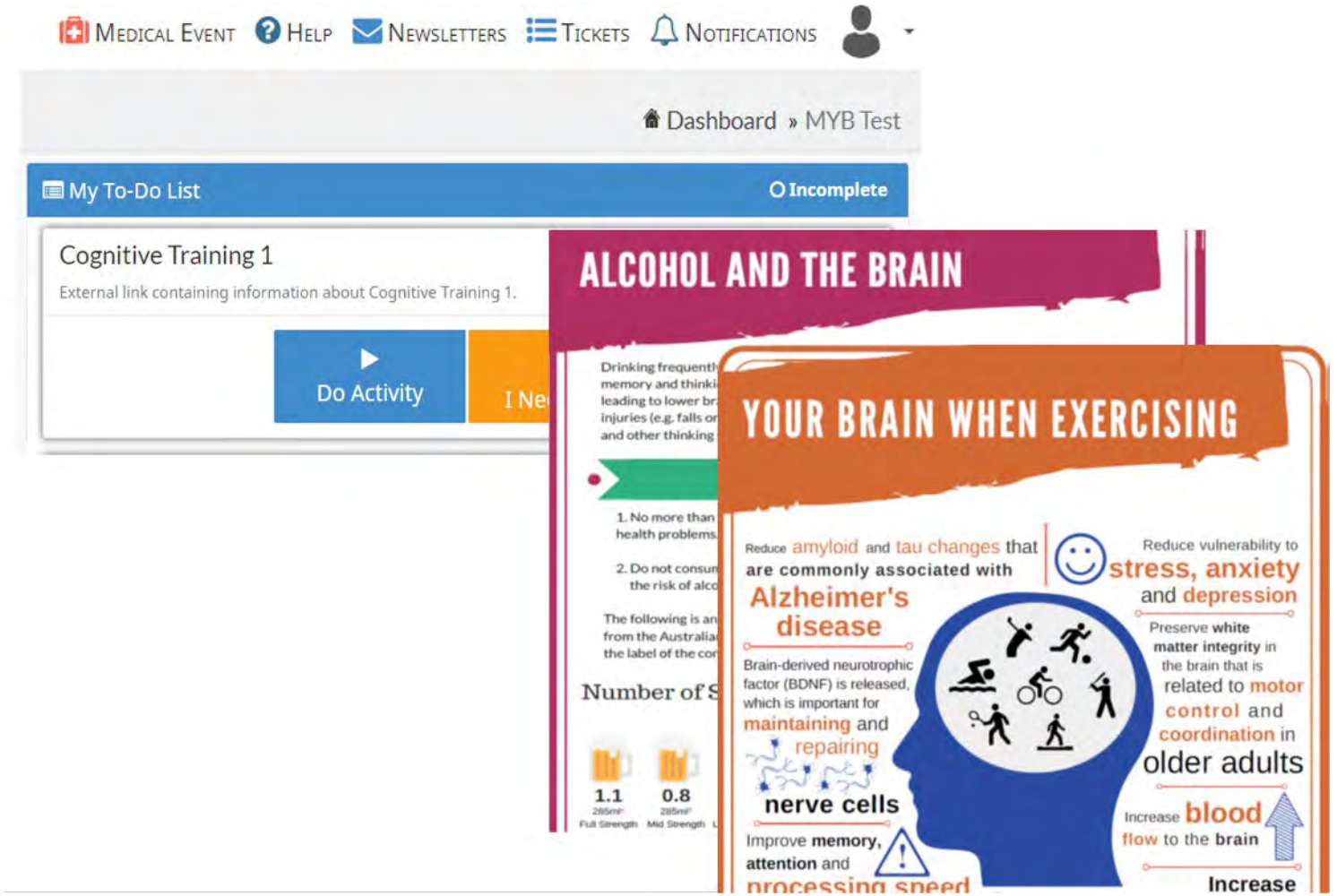
Information



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www.maintainyourbrain.org.au

- Almost 100,000 participants 55-77yo from 45 and Up study contacted → about 12,000 responded
- 6236 participants randomised – coaching or information
- Up to four modules depending on risk factors
- First year will finish in October 2019
- Boosters monthly for years 2 & 3
- If successful → less cognitive decline by Yr 3
- If more funding … less dementia by Yr 8

… interaction with genetic markers

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Drug studies

- Vaccines or enzyme inhibitors against Aβ
  - A4 Study
  - DIAN – TU
  - Alzheimer Prevention Initiative (Colombia)

Policy Implications

- Australia and the world is ageing
- 30 years of drug trials have failed to find a cure for Alzheimer's disease
- How will Australia cope with
  - … 430,000 people with dementia now and 1 million within 40 years?
  - … $14b+ or 1%GDP → 2% GDP
- Prevention or delay onset critical

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Policy Implications

- Can we prevent Alzheimer's and other dementias
- Not yet, but delay onset is possible
- 2- year delay → 20% reduction in prevalence
- 5-year delay → 50% reduction

Ideally delay till after ….

….

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Policy Implications

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Ideally delay till after ….

…. we die

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BE THE CHANGE!

- Population approach over whole of life
  - embryo/childhood may be most important
    - Especially education
  - Physical activity throughout life
    - never too early/ never too late
  - Healthy diet – plant based
  - Blood pressure control
- Health service approach
  - Prevention as primary care responsibility
  - Everyone's responsibility

the dementia momentum®

Invest in social change and help advance CHeBA's large-scale, 'big data' research.

BECOME A MEMBER OR FRIEND:

bit.ly/thedementiamomentum

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