Can we prevent Alzheimer’s disease?

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The challenge of Alzheimer’s disease

- Today about 55,000 suffer from dementia in New Zealand
- In 2050 there will be about 150,000
- Each year in NZ ~ 15,000 elderly develop dementia: ~ 40 every day
- Each year in NZ ~ 26,000 elderly develop memory impairment
- Cost ~ $1 billion per year

What causes Alzheimer’s disease?

- If it is age-related, then isn’t it - an inevitable part of ageing?
  
  NO, it is associated with specific changes in the brain, not found in everyone
  These changes lead the brain to shrink markedly

Alzheimer’s: a true disease

Healthy brain

Advanced Alzheimer’s

Hippocampus

So, to prevent Alzheimer’s we need to stop the brain from shrinking

What causes Alzheimer’s disease?

- If it is age-related, then isn’t it - an inevitable part of ageing?

  NO, it is a true disease

- ‘Anyway, it is all in the genes, isn’t it doctor?’

  NO, only 3 very rare genetic mutations are known to cause Alzheimer’s - less than 1% of all cases

Alzheimer’s disease is multifactorial

Inherited genes (< 1% of cases)
 NON-genetic risk factors

modifiable?

Many genes, mostly of small effect

Genetically-determined risk factors
Since risk factor reduction has worked for heart disease, will it also work for dementia?

Is the time-scale appropriate?

Alzheimer pathology develops slowly over many years until a threshold is reached.
Can we use this time-window to slow down progression of the disease by modifying risk factors?

Many of the postulated non-genetic risk factors for dementia are related to cardiovascular disease

How do we discover risk factors?

- Cross-sectional observational studies
- Prospective observational studies
- Randomised clinical trials - interventions to modify the risk factor

Topics for today

- Cardiovascular risk factors
  - Smoking
  - High blood pressure
  - Low physical activity
- Diet
  - Individual dietary factors
  - Dietary patterns
- Social and cognitive activity
- What can YOU do about it?
Cardiovascular risk factors in MID-LIFE and risk of AD 20 y later

Increases risk by approx. (up to) 650%

- Smoking       650%
- High blood pressure 30%
- High cholesterol 70%
- High homocysteine 110%
- Diabetes       40%
- Low physical activity 185%

Meng 2014

Leisure-time physical activity

Ask yourself this question, at age 50: "How often each week do you participate in leisure-time physical activity that lasts at least 20-30 mins and causes breathlessness and sweating?"

ACTIVE: Twice a week or more
SEDENTARY: Less than twice a week

Odds Ratio of Alzheimer’s disease 21 y later
0.35 (0.16-0.80) for the ACTIVE group
An apparent ~ 65% reduction in risk

CAIDE study, Finland n = 1,449, Rovio 2005

A randomized trial of exercise

Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease
A Randomized Trial

Meng 2014

JAMA 2008

• 170 - mild memory problems, 69y
• Controls: usual care
• Exercise: 50 min/day, 3 times weekly for 6 months

Exercise group showed improved global cognition and memory scores after 6 months, that were maintained for a further 12 months

Physical activity in elderly halves risk of AD
716 aged 88y; 71 developed AD. Wrist actigraphy for 10 days
Followed up for 5 years

Buchman 2012

Does diet influence the risk of AD?

- Individual dietary factors possibly protective
  - Anti-oxidant vitamins (C and E)
  - Fruit and vegetables
  - Flavonoids
  - Fish and omega-3 fatty acids
  - Vitamin D
  - Folate and B vitamins

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Flavonoid-rich foods and cognition
Semantic memory test in relation to foods consumed over previous year in 2,031 elderly

Nurk 2009, 2010

Eating fish protects against AD
Eating fish once or more each week reduces risk of AD by 33% compared with those who eat fish less than once a week.

Meta-analysis by Beydoun, 2014

B vitamins and homocysteine
Low-normal folate, low-normal B12 and high homocysteine are a risk factors for AD
High intake of folate protects against AD

Two trials have shown benefits of treatment with B vitamins in those with high homocysteine
- FACIT trial of folic acid in the Netherlands
- VITACOG trial of folic acid, B12 and B6 in people with Mild Cognitive Impairment (Oxford)

The shrinking brain
As we age (over ~ 60) the brain shrinks at a rate of ~ 0.5% per year, i.e. ~ 7 mL per year
Those of us with memory problems - 'mild cognitive impairment' or 'MCI' - show a faster rate of shrinkage of ~ 1.0% per year
In patients with Alzheimer's disease, the rate is higher still, at ~ 3% per year
Many risk factors for AD are associated with an increased rate of brain atrophy: smoking, diabetes, low omega-3, physical inactivity, low Med diet, high blood pressure, atrial fibrillation, high homocysteine, low B vitamins

Low vitamin D is a risk factor for dementia
1,658 US elderly aged 74

Conversion to dementia (%)

The shrinking brain
Serum B12 and change in brain volume

107 community-dwelling elderly, not impaired at baseline

% annual change in total brain volume over 5 years

r = 0.33
p < 0.001

Vogiatzoglou, OPTIMA, 2008

N.B. No-one was B12-deficient

Baseline vitamin B12 (pmol/L)

VITACOG trial (Oxford)

Preventing Alzheimer’s disease-related gray matter atrophy by B-vitamin treatment

Greeneville, Dossard, Belja Nefas, Celeste A. de Jager, Robin Jacoby, Thomas E. Nichols, Stephen M. Smith, and A. David Smith

PNAS 2013, 110:9523

- Subjects with Mild Cognitive Impairment were treated for 2 years with folic acid, B6 and B12
- In those with high homocysteine at baseline, the B vitamin treatment:
  - Slowed whole brain atrophy by 53%
  - Slowed atrophy of specific brain regions by 90%
  - Slowed, or stopped, further cognitive decline

VITACOG trial (Oxford)

Regions with significant atrophy over two years (P<0.001) in people with Mild Cognitive Impairment

- Medial temporal lobe

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Eating a Mediterranean diet protects from Alzheimer's disease

Scarmeas, 2006

Cumulative survival without Alzheimer's

2,258 elderly (77y): 262 incident AD cases

Strict adherence

Poor adherence

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Mediterranean diet

- High intake of
  - Vegetables & fruits
  - Legumes
  - Nuts
  - Cereals (unrefined)
  - Olive oil
  - Fish
- Moderate to low intake of
  - Dairy (mainly cheese, yoghurt)
  - Wine
- Less of
  - Meat and poultry

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Stimulating leisure activity is the key

Leisure activities and the risk of dementia in the elderly
Results from the Three-City Study  
Akharalay, Neurology 2009

5,698 over 65 y-old people followed for 4 y
Those who followed cognitively stimulating leisure activities more than twice a week had a 61% lower risk of AD:
- Cross-word puzzles
- Playing cards
- Artistic activity
- Attending organizations
- Cinema, theatre or concerts

Healthy Lifestyles Reduce the Incidence of Chronic Diseases and Dementia: Evidence from the Caerphilly Cohort Study
Peter Elwood1, Julia Astin2, Janet Pickering1, Stephen Polman1, Antony Bayes1, Yvonne Ben-Shlomo2, Marcus Langley1, John Gallacher7  
PLOS One 2013

2,235 men aged 45-59 followed for 25 years
Healthy behaviours defined as:
1. Not smoking
2. Consume > 3 portions fruit/veg per day
3. Consume < 30% of calories as fat
4. Physical activity: daily exercise
5. Alcohol < 3 units per day

Men who adopted 4 or 5 healthy behaviours had a 64% lower risk of dementia

USA Alzheimer’s Association 2015

"The evidence has now reached a point that it can no longer remain simply an exercise in academic discussion. The public should know what the science concludes:

Certain healthy behaviors known to be effective for diabetes, cardiovascular disease, and cancer are also good for brain health and for reducing the risk of cognitive decline."
Can we estimate the possible impact of the modification of risk factors?

Population attributable risk (PAR) estimates what proportion of AD might be attributed to a risk factor. It is based on the prevalence of the risk factor in the population and the size of the increase in risk.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PAR (%)</th>
</tr>
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<tbody>
<tr>
<td>High blood pressure</td>
<td>10</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>14</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>32</td>
</tr>
<tr>
<td>Smoking</td>
<td>31</td>
</tr>
<tr>
<td>Low education</td>
<td>24</td>
</tr>
<tr>
<td>High homocysteine (low B vits)</td>
<td>22</td>
</tr>
<tr>
<td>Low fish intake (omega-3)</td>
<td>22</td>
</tr>
</tbody>
</table>

N.B. do not add them up since there is overlap in an individual!

Meng 2014, Beydoun 2014

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Meng 2014, Beydoun 2014

Estimate that about half of AD is caused by known risk factors and that taking immediate action might prevent about one-fifth of predicted new cases by 2025

G8 dementia summit (2013)

Declaration from the Summit
"We recognise that dementia is not a normal part of ageing"

Communique from the Summit

History shows major diseases can be made manageable, even preventable, with sufficient political will.

We recognise the importance of taking a comprehensive and coordinated approach to the prevention of dementia, tailored to national and local needs, and to take prevention measures in the near term based on existing knowledge.

What can YOU do about it?

Practice prevention yourself: start young (40-50y)
- Stop smoking
- Exercise, at least 30 min brisk walk every day
- Take your high blood pressure and diabetes drugs
- Increase the 'Mediterranean' elements of the diet
  - Eat your 5-a-day of fruit and veg
  - Eat fish once, or more, a week
- Watch your blood glucose
- Make sure your vitamin D and B12 status are good
- Memory problems? Check your homocysteine and, if high, take B vitamins (consult GP)
- Keep active mentally and socially

Can we prevent Alzheimer's disease?

The answer is......

YES, we CAN