

A selection of slides from the lecture

Can we prevent Alzheimer's disease?

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University of Oxford
BRNZ Inaugural Public Lecture

Auckland, 3 February 2016



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?

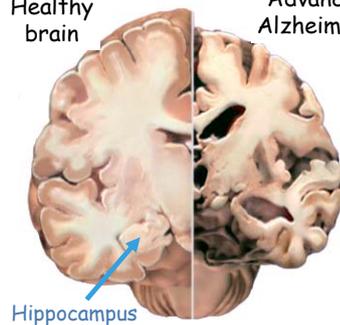
- If it is age-related, then isn't it - an inevitable part of ageing?

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



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?

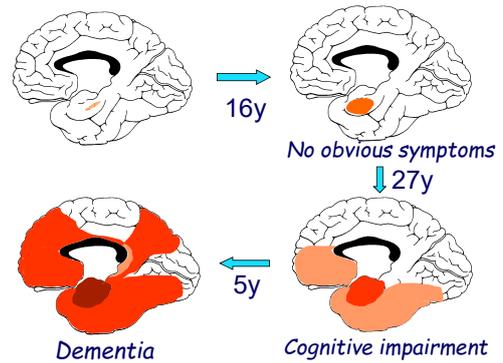
Many genes, mostly of small effect

Genetically-determined risk factors

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

Is the time-scale appropriate?

Spread of Alzheimer neurodegeneration - tangles

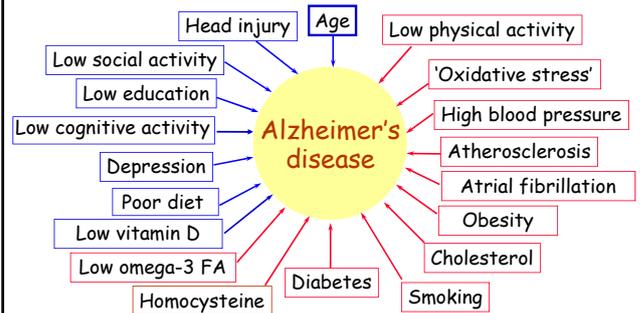


Smith 2002

Alzheimer pathology develops slowly over many years until a threshold is reached.

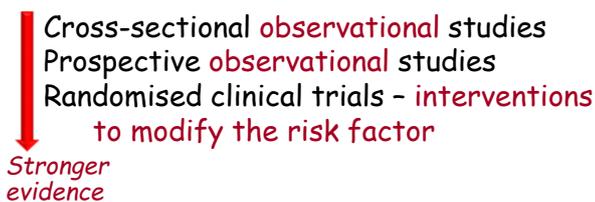
Can we use this time-window to slow down progression of the disease by modifying risk factors?

Postulated non-genetic risk factors for Alzheimer's disease



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

How do we discover risk factors?



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. |
| • Smoking | (up to) 650% |
| • High blood pressure | 30% |
| • High cholesterol | 70% |
| • High homocysteine | 110% |
| • Diabetes | 40% |
| • Low physical activity | 185% |

Meng 2014

A randomized trial of exercise

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

A Randomized Trial

JAMA 2008

Nicola T. Lautenschlager, MD
 Kay L. Cox, PhD
 Leon Flicker, MBBS, PhD
 Jonathan K. Foster, DPhil
 Frank M. van Bockxmeer, PhD
 Jiaqiao Xiao, MD, PhD
 Kathryn R. Greenop, PhD
 Osvaldo P. Almeida, MD, PhD

- 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

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

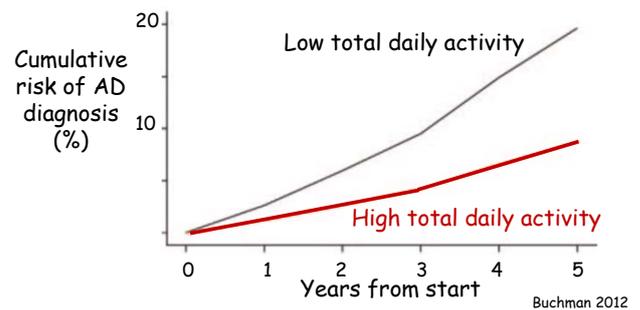
Odds Ratio of Alzheimer's disease 21 y later
 0.35 (0.16-0.80) for the ACTIVE group

An apparent ~ 65% reduction in risk

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

Physical activity in elderly halves risk of AD

716 aged 81y; 71 developed AD. Wrist actigraphy for 10 days
 Followed up for 5 years



Topics for today

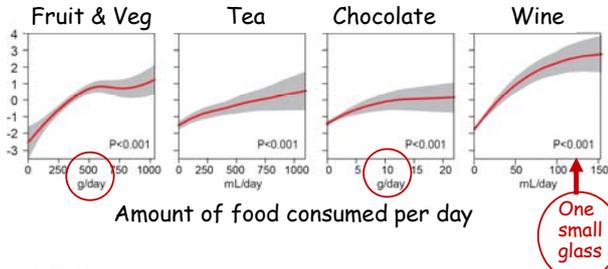
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Does diet influence the risk of AD?

- 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

Flavonoid-rich foods and cognition

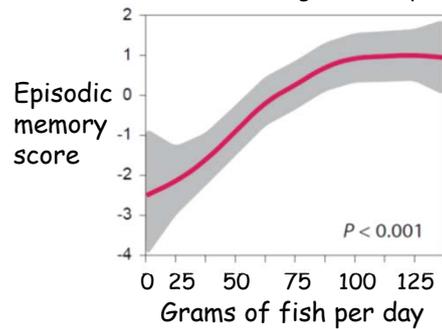
Semantic memory test in relation to foods consumed over previous year in 2,031 elderly



Nurk 2009, 2010

Cognition in the elderly: intake of fish

2,027 Norwegian elderly



Nurk, 2007

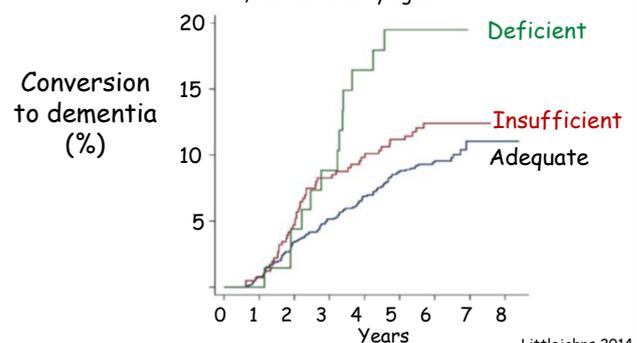
Eating fish protects against AD

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

Low vitamin D is a risk factor for dementia

1,658 US elderly aged 74



Littlejohns 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

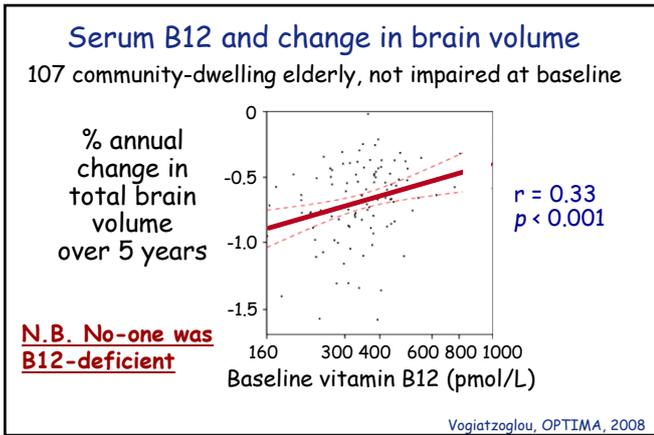
Two trials have shown benefits of treatment with B vitamins in those with high homocysteine

- 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**

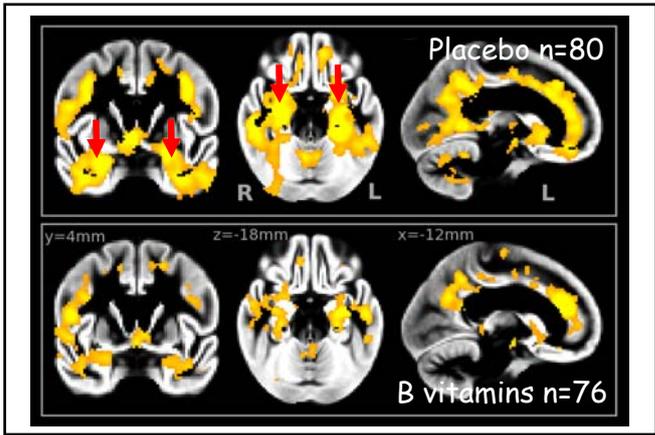
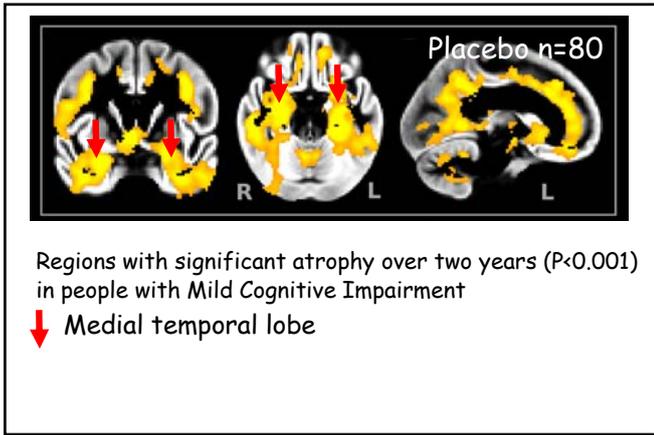


VITACOG trial (Oxford)

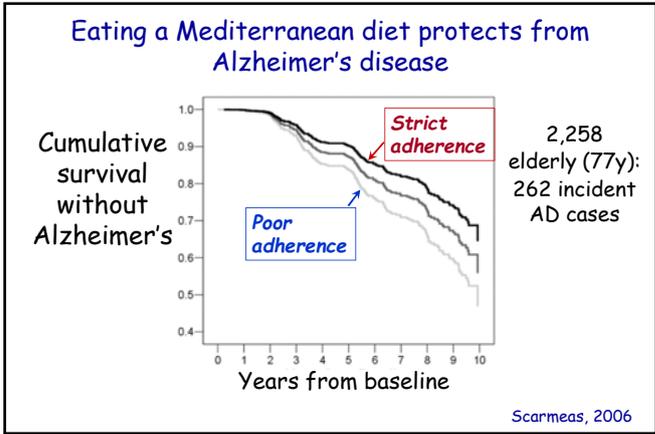
Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment

Gwenaëlle Douaud^{a,b,1}, Helga Refsum^{b,c,d}, Celeste A. de Jager^e, Robin Jacoby^a, Thomas E. Nichols^{a,f,g}, Stephen M. Smith^a, and A. David Smith^{b,h}
 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



- ### Topics for today
- Cardiovascular risk factors
 - Smoking
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 - Individual dietary factors
 - **Dietary patterns**
 - Social and cognitive activity
 - What can YOU do about it?



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 Akbaralay, *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

Lifestyle and dementia

Review

An active and socially integrated lifestyle in late life might protect against dementia

Laura Fratiglioni, Stephanie Paillard-Borg, and Bengt Winblad
Karolinska Institute, Stockholm

For all three lifestyle components (social, mental, and physical), a beneficial effect on cognition and a protective effect against dementia are suggested.

Taking into account the accumulated evidence and the biological plausibility, we conclude that an active and socially integrated lifestyle in late life protects against dementia and AD.

THE LANCET Neurology Vol 3 June 2004

Healthy Lifestyles Reduce the Incidence of Chronic Diseases and Dementia: Evidence from the Caerphilly Cohort Study

Peter Elwood¹, Julieta Galante¹, Janet Pickering¹, Stephen Palmer¹, Antony Bayer¹, Yoav Ben-Shlomo², Marcus Longley³, John Gallacher¹
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."

Baumgart 2015

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.

	PAR (%)
• High blood pressure	10
• High cholesterol	14
• Physical inactivity	32
• Smoking	31
• Low education	24
• High homocysteine (low B vits)	22
• Low fish intake (omega-3)	22

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

Meng 2014, Beydoun 2014

Letter

Journal of Alzheimer's Disease 38 (2014) 699–703

Dementia (Including Alzheimer's Disease) can be Prevented: Statement Supported by International Experts

On the occasion of the G8 dementia summit in London on 11 December 2013, we call upon the governments of the G8 countries to make *prevention of dementia* one of their major health aims.

Signed by 111 scientists from 36 countries

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"

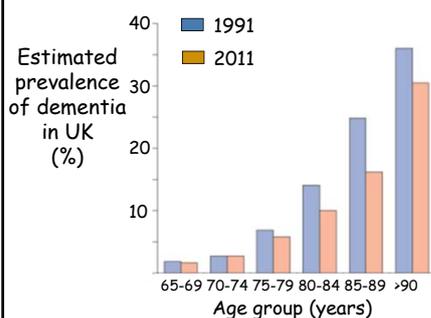
Communique from the Summit

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.

Has modification of risk factors already had some impact?

YES, in the UK



- 214,000 fewer cases in 2011 than predicted from 1991 data
- **24% decline**
- Possibly due to
 - reduction in CVD risk factors?
 - better diet?

Matthews 2013

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