The Importance of Longitudinal Epidemiological Research

Deciphering the secrets of diseases with long prodromes

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GAICD, PhD, FRACP, MBBS, BSc(Hons)
Director of the Women’s Healthy Ageing Project
Disclosures

• on the Board of Executive Directors for the Western Health Service, Victoria

• may accrue revenue from patent; pharmacogenomic diagnostic assay for seizure prediction,

• has been a paid clinical consultant and speaker for the Australian Commonwealth, Pfizer, Sanofi, other relationships subject to confidentiality clauses

• has been a chief investigator on investigator driven research projects receiving funds from Bayer, Merck, Piramal and GE Healthcare.
To understand Chronic Disease we need **Long** research follow-up
Chronic Disease

• “diseases of long duration and generally slow progression”\(^1\)

• Diseases with a long prodrome
  – importance of the timing and duration of required intervention/prevention
  – crucial in determining disease outcome.

• Without longitudinal studies of appropriate duration
  – the optimal timing and duration of intervention cannot be determined
  – may result in negative trials for otherwise appropriate therapies

\(^1\) World Health Organisation International
**Cross Sectional Study**

- **Year**: 1990, 1991
  - **Cohort Age (range)**: 45-55
  - **Study Size**: n = 2000
  - **Government Factors**: Bone Health, Cardiovascular, Diabetes, Mental Health

- **Mid-Life**
  - **Year**: 2001
  - **Cohort Age (mean)**: 55-65
  - **Study Size**: n = 438
  - **Target Group for Mid-life**: Risk factors and prevention. Active, healthy workforce
  - **Pension and Workforce Issues**: Morbidity & Quality of Life, Functional Status, Cognitive change

- **Early Ageing**
  - **Year**: 2011
  - **Cohort Age (range)**: 65-75
  - **Study Size**: n = 300
  - **Risk of Alzheimer’s Disease**: Doubles every 5 years after 65

- **Ageing**
  - **Year**: 2021
  - **Cohort Age (range)**: 75-80

**Government Factors**

- **WHAP**
  - **Study Areas**:
    - Mood & Wellbeing
    - Musculoskeletal / Bone
    - Arthritis
    - Muscle
    - Osteoporosis
  - **MWMHP**
    - Bone Health
    - Menopause
    - Mood / Wellbeing
    - Cancer
    - Weight
    - Morbidity & Quality of Life
    - Functional Status
    - Cognitive
    - Diabetes / Vascular Disease
    - Cardiovascular
    - Lifestyle

**Retirement**

- Cognitive change: 67% return
- Lifespan change: 58% return
- 200 people back so far
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Retention | 87%   | 74%   | 71%   | 58%   |
- **COGNICTION**: 4 times over 15 yrs

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- **CLINICAL, PSYCH**: 12 times over 22 yrs

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- **LIFESTYLE, PHYSICAL**: 11 times over 22 yrs

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- **BIOMARKER, STORED SPEC**: 11 x over 22 yrs

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- **BRAIN IMAGING MRI, FMRI, 18F Florbetaban**

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Example of therapeutic window
Cognition as an example of chronic disease with a long prodrome
Brain cell loss over time before diagnosed disease which occurs over 65 years of age
Is there evidence that the timing of intervention is important?
Figure. Relationship between outcome and age of participants in studies of the effect of cholesterol on dementia risk and progression. For each balloon, the left-most end is positioned at the mean age of participants at study start, the width represents the follow-up time, and the height indicates the cohort size. Red signifies a positive correlation of cholesterol level with dementia risk, gray a negative correlation, and blue no correlation. An additional study by Whitmer and colleagues is excluded because the large size of its cohort and long follow-up period would have distorted the figure.

Shepardson, Shankar, Selkoe (2011), Arch Neurology, 68 (10), 1239-44
Have we made mistakes examining only over 65’s before
TIMING OF THERAPY

• >200 research publications
  – oestrogen has a favourable effect on brain tissue, physiology and cognition in later life.

• Large Women’s Health Initiative memory study (WHIMS)
  – oestrogen supplementation did not improve cognition when initiated in women >65 years
    (Resnick, Maki et al 2005).
<table>
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<tr>
<th>Mortality, heart failure, or myocardial infarction</th>
<th>Hazard ratio (95% CI)</th>
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<tr>
<td>Age ≥50</td>
<td>0.48 (0.26 to 0.87)</td>
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<tr>
<td>Age &lt;50</td>
<td>0.63 (0.29 to 1.36)</td>
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<tr>
<td>Had a hysterectomy</td>
<td>0.32 (0.10 to 1.00)</td>
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<tr>
<td>Has an intact uterus</td>
<td>0.35 (0.13 to 0.89)</td>
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### Mortality

| Age ≥50                                           | 0.57 (0.30 to 1.08)  |
| Age <50                                          | 0.57 (0.30 to 1.08)  |
| Had a hysterectomy                                | 0.73 (0.31 to 1.68)  |
| Has an intact uterus                              | 0.43 (0.16 to 1.14)  |

| Had a hysterectomy                                | 0.29 (0.08 to 1.06)  |
| Has an intact uterus                              | 0.75 (0.36 to 1.59)  |
National Position Statement

Diagram:
- No or local progestogen
- Initiation long after menopause
- Initiation at menopause
- Systemic progestogen
- Less risk
- More risk
- Benefit
- Risk

Legend:
- +
- -
Estrogen therapy: is time of initiation critical for neuroprotection?

Barbara B. Sherwin


Abstract | According to the ‘critical period’ hypothesis, which attempts to explain the observed discrepancies in the studies on estrogen and cognition, estrogen therapy effectively decreases cognitive decline in aging women when it is initiated around the time of menopause but not when it is started decades later. Here, I review studies in which the timing of the initiation of estrogen therapy was provided, to determine whether their findings support the ‘critical period’ hypothesis. The vast majority of the reviewed studies support the idea that early but not late initiation of estrogen therapy might prevent or delay cognitive decline in aging women. Nevertheless, numerous design issues, such as the specific drugs and doses that were used, the possible effects of progestins on cognition, and the failure to administer neuropsychological tests of specific cognitive domains that are sensitive to estrogen therapy confound the extant literature. In view of the reanalyses of the Women’s Health Initiative’s data that show a beneficial effect of estrogen therapy on cardiac and breast diseases in women aged 50–59 years, more definitive evidence is needed to confirm that the early initiation of estrogen therapy that is continued for a few years provides enduring protection against cognitive aging 15–20 years later.
How long before revision?
Review

Hormone replacement therapy and the association with coronary heart disease and overall mortality: Clinical application of the timing hypothesis

Howard N. Hodis, Wendy J. Mack

\(^{a,b,1}\)

\(^{a}\) Keck School of Medicine, University of Southern California, 2250 Alcazar Street, CSC 132, Los Angeles, CA 90033, United States

\(^{b}\) Keck School of Medicine, University of Southern California, 2001 Soto Street, SSB 202Y, Los Angeles, CA 90033, United States

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**HT RCTs**

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**RUTH**

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The Women's Healthy Ageing Project

THE UNIVERSITY OF MELBOURNE
Earlier Detection of Alzheimer's Disease

NIH Public Access
Author Manuscript

Published in final edited form as:

Early Diagnosis of Alzheimer’s Disease: Is MCI Too Late?

Ronald C. Petersen, Ph.D., M.D.
Alzheimer's Disease Research Center, Mayo Clinic College of Medicine, Rochester, Minnesota

10. Emerging pharmacological therapies for MCI 233

cognitive decline between the prednisone and placebo treatment groups. Thus, a low-dose regimen of prednisone does not seem to be useful in treating Alzheimer’s disease. Again this suggests that there is a (as yet unknown) critical period for treatment, and MCI is simply too late a stage to intervene with this medication.
Those with amyloid show greater reduction in brain volume over time.

**10-year % Change in Hippocampal Volume**

- **FBB SUVR Negative/Positive**
  - p=0.2
  - % Change
    - Negative: -7.5
    - Positive: -18.6

- **FBB SUVR Low/Intermediate/High**
  - p=0.1
  - % Change
    - <1.2: -6.1
    - 1.2-1.5: -9.1
    - >1.5: -18.6


The Women’s Healthy Ageing Project: Fertile ground for investigation of healthy participants ‘at risk’ for dementia

CASSANDRA E. I. SZOEKE1,2, JOANNE S. ROBERTSON1,2, CHRISTOPHER C. ROWE3,3, PAUL YATES1,3, KATHERINE CAMPBELL1, COLIN L. MASTERS2, DAVID AMES4, LORRAINE DENNERSTEIN5,5 & PATRICIA DESMOND6
Earlier Detection of Alzheimers Disease

When is earlier – MCI?

Our Study says more than a decade amyloid positive even with normal cognition
No relationship in those over 65 doesn’t mean no relationship at any time in life
No relationship between vascular risk and amyloid

Cardiovascular risk factors, cortisol, and amyloid-β deposition in Alzheimer’s Disease Neuroimaging Initiative

Jon B. Toledo\textsuperscript{a,b,c}, Estefanía Toledo\textsuperscript{d}, Michael W. Weiner\textsuperscript{e,f,g}, Clifford R. Jack Jr.\textsuperscript{h}, William Jagust\textsuperscript{i}, Virginia M.-Y. Lee\textsuperscript{a,b,c}, Leslie M. Shaw\textsuperscript{a,b,c,*}, and John Q. Trojanowski\textsuperscript{a,b,c,*} for the Alzheimer’s Disease Neuroimaging Initiative
Interaction of Midlife PROCAM tertile x APOE ε4 status significantly associated with late-life FBB SUVR (p=0.04).

- ie. the association of high vascular risk tertile with Aβ was greatest in ε4+
- age and years of education.
The need for detailed studies in chronic diseases
ABNORMAL METABOLISM INCREASES RISK FOR ALZHEIMER’S DISEASE

- DNA POLYMORPHISMS AND MUTATIONS FACILITATE ABNORMAL METABOLISM (EJ. APOE4)
- MITOCHONDRIAL MEMBRANE DAMAGE AND FREE RADICALS PRODUCTION
- ABNORMAL PROTEIN SYNTHESIS, CLEARANCE AND DEPOSITION
- INADEQUATE CHOLESTEROL AND LIPIDS INTAKE
- PROSTAGLANDIN AND HORMONE DISBALANCES

RISK INCREASE

LIFESTYLE
- INFLAMMATION
- LESION TO AXONAL MYELIN AND ENDOTHELUM FAVOURS AMYLOID AND TAU DEPOSITS

EXPOSURES

NUTRITION

SOCIAL ENGAGEMENT

THE UNIVERSITY OF MELBOURNE

THE WOMEN'S HEALTHY AGEING PROJECT
But will such risk factor modification have an effect on disease?
The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence

Over Half of Alzheimer's Cases May Be Preventable, Say Researchers

By Steve Tokar on July 19, 2011 | Email | Print

Over half of all Alzheimer's disease cases could potentially be prevented through lifestyle changes and treatment or prevention of chronic medical conditions, according to a study led by Deborah Barnes, PhD, a mental health researcher at the San Francisco VA Medical Center (SFVAMC).

Analyzing data from studies around the world involving hundreds of thousands of participants, Barnes concluded that worldwide, the biggest modifiable risk factors for Alzheimer's disease are, in descending order of magnitude, low education, smoking, physical inactivity, depression, mid-life hypertension, diabetes and mid-life obesity.

The study results were presented at the 2011 meeting of the Alzheimer's Association International Conference on Alzheimer's Disease in Paris, France, and published online on July 19, 2011 in Lancet Neurology.
Summary

• Long prodromes can only be understood with long follow-up
• Timing of intervention is important
• We have made mistakes on this before by only examining populations for intervention over 65
• Such mistakes take decades to rectify
• Current Australian dementia studies recruit over 60 years of age – this precludes truly “early” detection
• Risk factors can have different effects on disease over the lifespan
• Modification could halve the cases of dementia
Need lifespan research

- Understand the full disease prodrome
- Therapeutic window
- Reversible, Irreversible effects
- Cumulative (capacity to make late life changes to offset earlier life)
- In diseases of ageing in research populations
  - (ageing studies recruit over 65)
Participants and their families

WHAP
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alz.org® alzheimer’s association
CogState
Bayer
Austin Health

The Florey Institute
of Neuroscience & Mental Health

The Melbourne Institute
of Brain Ageing

The Women’s Healthy Ageing Project

The University of Melbourne

Piramal
knowledge action care
Women

• Increased incidence of AD in women
  – Twice as likely as men the same age to develop dementia (Association, 2014).
  – Of the 5 million US cases of AD, two thirds were women (Association, 2014).

• Women have more severe disease and rapid decline (Holland, Desikan et al, 2013) than age matched men.
Review

Amyloid-β and Cognition in Aging and Alzheimer’s Disease: Molecular and Neurophysiological Mechanisms

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Abstract. Amyloid-β (Aβ) deposition in the brain is one of the key pathological features of Alzheimer’s disease (AD). Neither traditional clinical-pathological studies nor modern in vivo biomarker investigations of brain amyloid load, however, could reveal a convincing relationship between brain Aβ load and cognitive deficits and decline in patients with AD. Evidence suggests that pathophysiological Aβ dysregulation and accumulation are very early events that precede the onset of cognitive impairment reaching a plateau at the clinical stage of the beginning dementia syndrome. Therefore, research efforts have focused on the role of Aβ in asymptomatic older adults: the results of combined amyloid-PET and neuropsychological studies show a modest but significant correlation between brain fibrillar amyloid load and various subtle cognitive deficits, most notably in challenging episodic associative memory tasks. In order to elucidate the pathophysiological link between cognition and Aβ, a number of combined functional neuroimaging studies have been performed, resulting in early and complex functional alterations in cognitively relevant neural networks such as the default mode network and the largely overlapping episodic memory networks.
Women

- CSF Ab42 reduction correlating with memory in female healthy elderly but not in males
- Amyloid load on Pib scans relating to cognition in women but not men *Pike et al, 2011, Neuropsychologica*