Prevention Strategies for Alzheimer’s Disease & other late-life dementias

Lefkos T Middleton, MD, FRCP
Imperial College London
Population Ageing is a global challenge

Percentage aged 60 years or over by region, 1980–2050

...And the population over 80 is growing even more...

Population aged 80 or over: world, 1950-2050

- 2050: 379.0 million
- 2025: 153.4 million
- 2000: 69.2 million
- 1975: 31.4 million
- 1950: 13.8 million

First Reported Patient with Alzheimer's disease
Alzheimer’s disease

• 1st leading cause of death in the world
• 36 M patients world-wide- expected to raise to >80 M by 2050
• Affects ~ 3-5% at 65, prevalence doubles every 5 years to reach ~40 + 80 years of age
• Rarely familial
Exponential Increase of World-wide Dementia Care Costs...

• Have escalated from $603 Billion (in 2010) to $818 Billion (in 2014)

• Will be over a trillion by 2018

• In a decade?

Alzheimer Disease International 2015 annual report
Yearly Costs of Dementia Care

- US: USD 160-215 billion
- EU: Eur 160 billion
- UK: StP 26 billion

Dementia US Costs vs:

- Cancer Care: USD 77 billion
- Heart disease: USD 102 billion
Acknowledgments

Perspective

Why has therapy development for dementia failed in the last two decades?

Serge Gauthier\textsuperscript{a}, Marilyn Albert\textsuperscript{b}, Nick Fox\textsuperscript{c}, Michel Goedert\textsuperscript{d}, Miia Kivipelto\textsuperscript{e}, Jorge Mestre-Ferrandiz\textsuperscript{f}, Lefkos T. Middleton\textsuperscript{g,*}

\textsuperscript{a}Alzheimer’s Disease Research Unit/Memory Clinic, McGill Centre for Studies in Aging, Montreal, Quebec, Canada
\textsuperscript{b}Division of Cognitive Neuroscience, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
\textsuperscript{c}Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK
\textsuperscript{d}Division of Neurobiology, MRC Laboratory of Molecular Biology, Cambridge, UK
\textsuperscript{e}Center for Alzheimer Research and Aging Research Center (ARC), Karolinska Institutet, Department of Geriatric Medicine Clinical Trials Unit, Karolinska University Hospital, Huddinge, Sweden
\textsuperscript{f}Office of Health Economics, London, UK
\textsuperscript{g}Neuroepidemiology and Ageing Research, School of Public Health, Imperial College London, London, UK
Drugs in active development by phase (dementia compared to all other therapy areas)

CTEG-OHE Attrition Analysis of Dementia R&D, 2015
Figure 2 | Attrition profiles across therapeutic areas. The funnels illustrate the average number of compounds needed at each development stage to result in one launched drug for hepatitis C virus infection, Alzheimer disease and antibacterial indications that include infections due to methicillin-resistant Staphylococcus aureus (MRSA). The preclinical stage includes lead optimization and preclinical phases, and the overall success rate from discovery to launch assumes 60% success rate in the discovery stage. Sources: *Paul et al. (Nature Rev. Drug Discov. 9, 203–214; 2010); Pharmaprojects; EvaluatePharma; BCG analysis; see Supplementary information S1 (box) for details.
Major Gaps in our understanding of the disease

- **One or many more diseases?** Disease Heterogeneity, lack of effective diagnostic & prognostic biomarkers.
- **75% of dementia patients, over >75 years of age, have mixed pathologies.**
- Etiology and physiopathology neither linear nor additive but, *like a ballet*, choreographed interactively over time.
- **Complex aetiology**, involving genomic, epigenetic, expression and a multitude of *evolving* environmental factors.
Disease Course
Pathology vs Clinical Disease

Onset of pathology

Cognitive performance

Asymptomatic phase?
Risk prediction

5-10 years
Clinical phase

Onset of symptoms
(MCI- AD diagnosis)

100%

Time

Tau/ amyloid & atrophy

Imperial College London
Unravelling Disease Complexity: We now have the tools

Common Diseases are Complex & Heterogeneous

- Epidemiology
- Clinical Manifestations
- DNA variation - RNA-omics
- Imaging
- Systems Biology

Understand & better Define Disease
- New Targets
- New drugs
- New indications

Biomarkers for Risk Prediction

Targeted Disease Phenotypes
The New NIA/AA (2017) Diagnostic Criteria for Alzheimer’s Disease (AD) will define AD on Biomarker Evidence of Abnormal Amyloid & Tau Brain Load.
**APOE 4 is strongest Genetic Risk Factor for late onset Dementia and for brain Accumulation of Amyloid in AD**

Kaplan-Meier survival curves: AD onset by age and APoE 2,3,4 alleles

*Hao et al, 2007*
Defining Disease Prevention

• **Primary prevention** aims to prevent disease or injury before it ever occurs. This is done by preventing exposures to hazards that cause disease or injury, altering unhealthy or unsafe behaviours that can lead to disease or injury, and increasing resistance to disease or injury should exposure occur. Examples include:
  - immunization against infectious diseases, lifestyle changes to prevent CV disease

• **Secondary prevention** aims to reduce the impact of a disease or injury that has already occurred. This is done by detecting and treating disease or injury as soon as possible to halt or slow its progress and implementing programs to return people to their original health and function to prevent long-term problems. Examples include:
  - regular exams and screening tests to detect disease in its earliest stages (e.g. mammograms to detect breast cancer)
  - daily, low-dose aspirins and/or diet and exercise programs to prevent further heart attacks or strokes

• **Tertiary prevention** aims to soften the impact of an ongoing illness or injury that has lasting effects. This is done by helping people manage long-term, often-complex health problems and injuries in order to improve as much as possible their ability to function, their quality of life and their life expectancy. Examples include:
  - New Cancer therapies, cardiac or stroke rehabilitation programs, chronic disease management programs.
Modifiable Protective & Risk Factors for AD
Prevention: Optimal Timing for Intervention

Jack et al, Lancet Neurol 2010
Potential for Primary Prevention for Alzheimer’s disease-based on Seven Modifiable Risk Factors: Diabetes, midlife Hypertension & Obesity, Physical Inactivity, Depression, Smoking and Low Education:

Up to 30% Reduction of Disease Incidence

Interpretation After accounting for non-independence between risk factors, around a third of Alzheimer’s diseases cases worldwide might be attributable to potentially modifiable risk factors. Alzheimer’s disease incidence might be reduced through improved access to education and use of effective methods targeted at reducing the prevalence of vascular risk factors (eg, physical inactivity, smoking, midlife hypertension, midlife obesity, and diabetes) and depression.

Norton et al, Lancet Neurol, 2014
Systematic evaluation of the associations between environmental risk factors and dementia: An umbrella review of systematic reviews and meta-analyses


- Chronic Benzodiazepines use
- Depression at any age, late-life depression
- Frequency of social contacts for all types of dementia
- Late-life depression for Alzheimer's disease
- Type 2 diabetes mellitus for vascular dementia and Alzheimer's disease.
Figure: Projected percentages of Alzheimer’s disease cases that could be prevented, with 10% or 20% reductions per decade in each risk factor

Norton et al, Lancet Neurol, 2014
Fig. 1. Kaplan–Meier survival estimates from baseline to dementia occurrence by APOE ε4 in combination with education, vascular risk factors, and leisure activities (adjusted for age and sex). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

Ferrari et al, 2012
Lifestyle Trial Intervention Schedule

**INTENSIVE MULTIDOMAIN INTERVENTION**

- **NUTRITION:**
  - 7 group sessions,
  - 3 individual sessions

- **EXERCISE:**
  - 1-2x/wk muscle
  - 2-4x/wk aerobic

- **EXERCISE:**
  - 2x/wk muscle
  - 4-5x/vk aerobic

- **EXERCISE:**
  - 2x/wk muscle strength training
  - 5-6x/wk aerobic training

- **COGNITIVE TRAINING:**
  - 9 group sessions
  - Independent training

- **COGNITIVE TRAINING:**
  - 2 group sessions
  - Independent training

**MONITORING AND MANAGEMENT OF METABOLIC AND VASCULAR RISK FACTORS**

- Nurse: Visit every 3 months
- Physician: 3 additional visits

**MINI-INTERVENTION**

**REGULAR HEALTH ADVICE**

*Kivipelto et al., Alzheimer & Dementia 2013*
Primary efficacy outcome: global cognition

(NTB composite Z score)

Intervention group: 25% higher improvement

Difference between intervention and control groups per year:
Estimate (95% CI) = 0.022 (0.002-0.042)
p=0.03

Lines = estimates for cognitive change from baseline to 12 and 24 months
Higher scores = better performance
Error bars = standard errors
P-values = difference in trajectories over time between groups

*Kivipelto, Ngandu, Solomon et al., Lancet 2015*
Is dementia incidence declining? Trends in dementia since 1990 in the Rotterdam study

<table>
<thead>
<tr>
<th>Age stratum, y</th>
<th>Total</th>
<th>Man</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate 1990</td>
<td>6.56</td>
<td>6.25</td>
<td>6.78</td>
</tr>
<tr>
<td>Incidence rate 2000</td>
<td>4.92</td>
<td>4.48</td>
<td>5.20</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>0.75 (0.56-1.02)</td>
<td>0.72 (0.44-1.16)</td>
<td>0.77 (0.52-1.14)</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate 1990</td>
<td>1.29</td>
<td>1.76</td>
<td>0.90</td>
</tr>
<tr>
<td>Incidence rate 2000</td>
<td>1.08</td>
<td>1.39</td>
<td>0.82</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>0.83 (0.29-2.41)</td>
<td>0.79 (0.20-3.08)</td>
<td>0.91 (0.17-4.94)</td>
</tr>
<tr>
<td>70-79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate 1990</td>
<td>9.66</td>
<td>9.81</td>
<td>9.49</td>
</tr>
<tr>
<td>Incidence rate 2000</td>
<td>6.36</td>
<td>4.69</td>
<td>7.82</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>0.66 (0.40-1.10)</td>
<td>0.48 (0.21-1.11)</td>
<td>0.82 (0.43-1.56)</td>
</tr>
<tr>
<td>80-89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate 1990</td>
<td>31.46</td>
<td>30.93</td>
<td>31.75</td>
</tr>
<tr>
<td>Incidence rate 2000</td>
<td>26.42</td>
<td>20.41</td>
<td>24.22</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>0.84 (0.56-1.26)</td>
<td>0.98 (0.51-1.90)</td>
<td>0.77 (0.45-1.29)</td>
</tr>
</tbody>
</table>

Schrijvers et al, 2012
Age - Specific Dementia Prevalence
CFASI and II (1989-94 and 2008-11)

Matthews et al, 2013
Dementia Incidence Rates in Men and Women

Matthews et al, 2016
A few words about EIT Health & the CARE Initiative (Caring and Ageing reimagined in Europe)
European Institute of Innovation & Technology - EIT Health
EU wide Industry – Academia Partnership
Established 2015

CLC UK/Ireland

CLC Belgium/Netherlands

CLC Spain

CLC France

CLC Germany

CLC Scandinavia

InnoStars
EIT Health mission & vision

EIT Health promotes entrepreneurship and develops innovations in healthy living and active ageing, providing Europe with new opportunities and resources.

EIT Health’s vision is to become a catalyst for change and a community which creates novel solutions that make healthy lives a reality for all.
EIT Health
A European Engine for Innovation for Healthy Ageing

Challenge 1
Promote Healthy Living

Challenge 2
Support Active Ageing

Challenge 3
Improve Health Care

Societal Challenges
Cross Challenges

A: Removing Barriers to Innovation
B: Leveraging Talents & Education
C: Leveraging enabling Technologies and exploiting (big-) Data

InnoLife Projects
InnoLife Accelerator
InnoLife Campus

Impact
Successful Start-ups
Better trained personnel
Globally competitive European industry
Faster market access and diffusion of innovative products and services

Strategic Outcomes
Better quality of life
Citizens enabled to take ownership of their health
Empowered citizens to take choices for longer active and social life
Improved patient pathways, cost-effectiveness and quality of healthcare
Stronger innovation eco-systems at CLCs and the InnoStars

Imperial College London
Elder caregiving is a massive and increasing unmet need of our 21st century.
Caring & Ageing Reimagined in Europe (CARE)
2016 CARE Landscape Analysis Report

CARE CAMPUS

A Landscape Analysis
Rising Need for Elder Care in Europe Necessitates New Paradigm for Elder Caregiving Training

Project supported by EIT Health
Caring & Ageing Re-imagined in Europe (CARE)

- CARE e-based School for Carers 2018
- CARE Weekly Open Access Journal 2017
- CARE Social Networking Platform 2018
- Landscape Analysis Report on Caring in Europe
There are four kinds of people in the world:
Those who have BEEN caregivers;
Those who currently ARE caregivers;
Those who WILL BE caregivers;
And those who will NEED caregivers

Rosalynn Carter
Former First Lady of the United States
GLOBAL POPULATION AGEING
An era of opportunities and challenges World-wide
Basic Copyright Notice & Disclaimer

©2017 This presentation is copyright protected. All rights reserved. You may download or print out a hard copy for your private or internal use. You are not permitted to create any modifications or derivatives of this presentation without the prior written permission of the copyright owner.

This presentation is for information purposes only and contains non-binding indications. Any opinions or views expressed are of the author and do not necessarily represent those of Swiss Re. Swiss Re makes no warranties or representations as to the accuracy, comprehensiveness, timeliness or suitability of this presentation for a particular purpose. Anyone shall at its own risk interpret and employ this presentation without relying on it in isolation. In no event will Swiss Re be liable for any loss or damages of any kind, including any direct, indirect or consequential damages, arising out of or in connection with the use of this presentation.