Preventing Dementia: A stepped approach towards 2020

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University of Edinburgh
PREVENT DEMENTIA

• STEP 1 – Recognize the extent of the problem
• STEP 2 – Understand disease before dementia
• STEP 3 – Characterize an individual’s risk
• STEP 4 – Personal and Public Intervention
Alzheimer's Disease

• AD a progressive neurodegenerative disorder that accounts for 60-80% dementia cases

• Early symptoms: Difficulty in remembering conversations, names or events; apathy and depression

• Late symptoms: Impaired communication, disorientation, confusion, behavior changes and, eventually, difficulty speaking, swallowing and walking

• Risk factors: Age, APOE-ε4 Gene, family history, cardiovascular disease risk factors, mild cognitive impairment, traumatic brain injury

• Total estimated cost of dementia is US$818 billion in 2015-represents 1.09% of global GDP
Alzheimer's Disease

- Amyloid Plaque
- Damaged Neuron
- Fibril
- Oligomers
- Presenilin
- Beta-amyloid
- Beta-secretase
- Gamma-secretase Complex
- Damaged Mitochondrion
- Disintegrating Microtubule
- sAPPβ
- sAPPα
- Tangle
- Tau Fragments
- Healthy Neuron
- Healthy Microtubule
- Healthy Mitochondrion
- Alpha-secretase
- Gamma-secretase Complex
Biomarkers and Alzheimer’s Dementia

- Amyloid Pathology
- Tau Pathology
- Cerebrovascular Changes
- $\alpha$-synuclein
- Blood Brain Barrier Integrity
- Glial activation and inflammation
- Oxidative stress
- Mitochondrial dysfunction
- Synaptic dysfunction
- Metal dyshomeostasis
- Apoptosis
- Insulin resistance
- mTOR signalling
- $\beta$-HSD function
Prevalence of dementia

Winblad B, Lancet Neurol 2016
Alzheimer's Disease

• Problems that need to be solved:

• No new treatments for AD for almost 20 years

• Who is at risk?

• How early can we identify people?
• Do people want to be identified?

• How do we move the science forward from embedded belief systems?
Ongoing clinical trials in Alzheimer disease (AD)

β amyloid

Aβ production
Aβ clearance
Aβ aggregation

Cholinergics
Others

More than 200 drug development failures in the last 30 years
Schneider Mangialasche, Kivipelto et al., JIM 2014

† Currently approved for AD treatment

Mangialasche, Kivipelto et al, modified 2013 from Lancet Neurology, 2010
Why do drugs fail?

1. Dementia is late stage disease

2. Treatments are too pathology-specific

3. Outcome measures are insensitive

4. Biomarkers don’t correlate with clinical features at individual level

5. The trials are badly prosecuted
Why focus on prevention?

- Brain changes occur many years before onset of symptoms
- No pharmacological agent is available which can either reverse or halt the progression of AD
- Risk factors for late-onset AD include older age, the APOE ε4 genotype, head injury, family history, low education and low participation in cognitively stimulating activities
- Modifiable risk factors are also involved, including cognitive stimulation, diet (vascular) and physical activity
- Delaying onset of dementia by 5 years would result in a 50% reduction in prevalence
Pathological Changes Before Onset of Clinical Disease

Biomarker changes observed in mutation carriers (PS1 and APP) registered in Dominantly Inherited Alzheimer’s Network (DIAN)

R Bateman NEJM 2012
Risk factors

Across the lifespan

Unhealthy diet
APOE, other genes
Familial aggregation
Dyslipidemia
Hypertension
Obesity
Dyslipidemia

0 20 60 75
Adult life Mid-life Late-life

Education Cognitive and social activity
Physical activity

Cognitive reserve
Brain reserve

Protective factors

Figure adapted from Sindi S, et al. F1000Prime Rep. 2015;7:50.
The Vision

• That any given individual from birth onwards can be given an accurate ‘probability’ of a neurodegenerative ‘event’
  – Dementia
  – Cognitive decline
  – Biomarker change

• We are making a ‘prognosis’ not a ‘diagnosis’
The Vision

• That any given individual from birth onwards can be given an accurate ‘probability’ of a neurodegenerative ‘event’
  – Dementia
  – Cognitive decline
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• We are making a ‘prognosis’ not a ‘diagnosis’
PROBABILITY MODELLING

One Dimensional Approach

Function:
Cognitive Activities of Daily Living

Thresholds:
Subjective Cognitive Impairment  X% probability decline
Mild Cognitive Impairment  2-15% probability
Dementia  99% probability
PROBABILITY MODELLING

Two Dimensional Approach

Biomarkers:
- Imaging
- CSF
- Blood-based

DuBois Criteria
NIA-AA Criteria
Cochrane Reviews

Greater Probability

Lesser Probability

Biomarker

Function
PROBABILITY MODELLING

Two Dimensional Approach

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- Imaging
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Biomarker

Greater Probability

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Biomarker

Greater Probability

Lesser Probability

Function
Two Dimensional Approach

Biomarkers:
- Imaging
- CSF
- Blood-based

Can Biomarkers be used in isolation in pre-clinical populations?

Greater Probability

Lesser Probability

Biomarker
PROBABILITY MODELLING

Three Dimensional Approach

Risk Factors:
- Age
- Genotype
- Head Injury
- Diabetes
- Depression
- Lifestyle

Biomarker

Risks

Function
PROBABILITY MODELLING

Three Dimensional Approach

Risk Factors:
- Age
- Genotype
- Head Injury
- Diabetes
- Depression
- Lifestyle

Biomarker

Risks

Function
PROBABILITY MODELLING

Biomarker

Current ‘State of Play’:
‘MCI due to AD’

Risks

Function
Risks

Caution – may be an inverse relationship.

Increasing amyloid may be associated with a decreasing probability as age (risk) increases.
Risks

PROBABILITY MODELLING

Biomarker

3 Dimensional Model
Incorporates all 3 dimensions in determining an individual's probability of decline

Every individual can be 'placed' in 3D space that can articulate a probability of decline

Risks

Function
PROBABILITY MODELLING

Incorporates all 3 dimensions in determining an individual's probability of decline.

Every individual can be ‘placed’ in 3D space that can articulate a probability of decline.
Disease Models for Brain Failure

• Need to accommodate:
  – Multiple disease processes
  – A new approach to outcomes
    • Spectrum versus categorical diagnosis/impairment
Alzheimer’s disease modelling in mid-life

- Proposes a linear sequence or cascade of events that are dependent.
- Primacy of amyloid pathology.
- More accurate model would incorporate multiple pathological processes where clinical phenotype not categorical
- Biomarkers would reflect these multiple disease processes.
- Interventions specific to early disease process or generic across pathologies?
- Every individual in pre-clinical phase can be put on a point on a probability spectrum
Different Profiles (Normal Ageing)

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<th>Processes</th>
<th>40-50</th>
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Different Profiles (Alzheimer’s dementia)

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Different Profiles (Alzheimer’s dementia)

TO TAKE THE NEXT BIG STEP

1. THE RIGHT and HIGHEST QUALITY DATA
2. THE RIGHT STATISTICAL APPROACH
3. ACCEPTANCE THAT WE ‘DON’T KNOW’

Specific interventions at a critical (early) time point on background of general approach to modification of risk...
EPAD
European Prevention of Alzheimer’s Dementia Consortium

www.ep-ad.org
EPAD Consortium: Member organisations

- Funded by IMI (Innovative Medicines Initiative)
- Managed and Sponsored by University of Edinburgh
- €64M Initial Grant
The European Prevention of Alzheimer's Dementia (EPAD) project aims to develop an infrastructure that efficiently enables the undertaking of adaptive, multi-arm Proof of Concept studies for early and accurate decisions on the ongoing development of drug candidates or drug combinations for the prevention of AD dementia.


AD, Alzheimer's disease; EPAD, European Prevention of Alzheimer's Dementia
EPAD objectives

• Develop a Platform to test treatments for the **Secondary Prevention of Alzheimer’s Dementia:**

  • Including delay of onset of Alzheimer’s dementia in
    • People at risk of developing Alzheimer’s dementia due to biological evidence of Alzheimer’s pathology; and
    • People with very early symptoms in addition to biological evidence of Alzheimer’s pathology (i.e. MCI due to AD or prodromal AD)

• Excluding
  • People with dementia
  • People who have no symptoms and no evidence of Alzheimer’s pathology (primary prevention population)


AD, Alzheimer’s disease; EPAD, European Prevention of Alzheimer’s Dementia; MCI, mild cognitive impairment
EPAD funnel
The EPAD PoC Trial

Allows early decisions on progression to longer term clinical outcomes by impact on pre-defined and target-specific intermediary phenotype.
Parent cohorts from UK/Ireland

Partners:

**PREVENT**
Generation Scotland
UK Biobank

Craig Ritchie
David Porteous
Cathie Sudlow
The PREVENT Programme:

- Aged 40-59
- Longitudinal cohort (Baseline and Year 2)
- Pilot phase (n=212)
- Edinburgh Site Recruitment (n=25)
- Oxford and Cambridge Site to open in 2016
- Target 700 participants by end 2016
## Risk Factors Captured in PREVENT

<table>
<thead>
<tr>
<th>Domain</th>
<th>Risk</th>
<th>Measure being used</th>
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<tr>
<td>Principal Risk Model</td>
<td>ApoE genotype</td>
<td>Genetic analysis</td>
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<td>Parental history</td>
<td>History from participant</td>
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<tr>
<td>Genetic</td>
<td>Genotype</td>
<td>e.g. Genome Wide Association Studies</td>
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<tr>
<td>Environmental</td>
<td>Diet</td>
<td>Scottish Food Frequency questionnaire</td>
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<td>(Scottish Collaborative Group, 2004)</td>
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<td>Life Events</td>
<td>Life Stressor Checklist - revised (Wolfe &amp; Kimerling, 1997)</td>
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<td>Sleep*</td>
<td>Pittsburgh Sleep Evaluation (Buysse et al., 1989)</td>
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<td>Exercise</td>
<td>Study Proforma</td>
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<td>Clinical</td>
<td>Head Injury</td>
<td>BISQ (Brain injury screening questionnaire, 2011)</td>
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<td>Inflammation**</td>
<td>Inflammatory Markers</td>
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<td>Cardiovascular</td>
<td>ECG/Pulse &amp; BP</td>
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<td>Depression*</td>
<td>CES-D (Radloff, 1977)</td>
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<td>Respiratory</td>
<td>Spirometry</td>
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<td>Stress</td>
<td>Salivary Cortisol / Resilience Questionnaire</td>
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<td>Diabetes / renal function</td>
<td>Standard haematology and biochemistry.</td>
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<td>/ Metabolic Syndrome</td>
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*May act as both risk for neurodegenerative disease and an outcome.

**May act as a risk factor for neurodegenerative disease and an expression of a core disease pathway.
Expressions of disease state in PREVENT Programme: Genes, biomarkers, cognition and language

• Imaging
  – fMRI with task, Magnetic Resonance Spectroscopy, Diffusion Tensor Imaging, vMRI, WML volume
  – Amyloid PET imaging via UKDP
• Cerebrospinal Fluid (30%)
  – Aβ/Tau (Discovery)
• Blood
  – Aβ, inflammatory markers, trace metals, micronutrients, lipids (Discovery)
• Saliva
  – Cortisol
• Cognition: COGNITO, Verbal Short Term Memory Binding Paradigm
EPAD Cohort

Consent

Trial Delivery Centre

AD
Mixed
Vascular
FTD
PDD
LBD
Family Hx

Imperial College London
West London Mental Health NHS Trust
University of Cambridge
University of Exeter
King’s College London
Alzheimer’s Society
University of Oxford

Research Programme
The EPAD Longitudinal Cohort Study

- **Maintained at N=6,000**

- **Data**
  - EPAD Cohort Baseline
    - Clinical
    - Biomarker
    - Imaging
  
  - 1st Follow Up
  
  - 2nd Follow Up

- **Loss to Follow Up**
- **Enter Other Clinical Trial**
- **Enter EPAD Trial**

- **Replenishment from Virtual EPAD Register**
The EPAD LCS Protocol

- Annual assessments
  - 6/12 Cognition Assessment

- EPAD Neuropsychological Evaluation (ENE)*
- Neuroimaging*
- 100% will give CSF Sample for Aβ/Tau (Gothenburg)
- Blood, urine and saliva for genomics (blood) and storage for exploratory biomarkers (Edinburgh)
- Safety labs done locally at the TDCs
- Clinical and other risk factors

www.ep-ad.org
Cognition (in order of administration)

RBANS (Primary)
- Verbal Episodic Memory: List Learning & Story Memory
- Visual Episodic Memory: Figure Recall
- Visuospatial/Constructional: Figure Copy & Line Orientation
- Language: Picture Naming
- Attention/Executive Functioning: Semantic Fluency, Digit Span, Coding

Four Mountains Task - (allocentric space; Exploratory)
Dot counting - (working memory; Secondary)
Flanker - (choice reaction time and set-shifting; Secondary)
Name/Face pairs - (paired associate learning; Secondary)
Supermarket Trolley Virtual Reality - (egocentric space; Exploratory)
Neuroimaging outcomes

Structural MRI
- Cortical thickness, deep GM volumes
- Fractional anisotropy (FA) of temporal lobe, diffusion kurtosis (multi b-value DTI), network alterations

Functional MRI
- Global & parietal CBF
- Changes within the default-mode network (DMN) & relation with hippocampal activity (rsfMRI)
- Bolus arrival time (multi-delay ASL)
- Network analysis (rsfMRI)

PET Amyloid Imaging
- To be confirmed in IMI2
May 3\textsuperscript{rd} expect First Research Participant to be Recruited into EPAD LCS.

Success of project predicated on close academic collaboration with Parent Cohorts across Europe and engagement with public on the vision of EPAD.

Forming a key part of the developing global network of aligning projects:
- GAP, CPAD, JPAD and APAD
Acknowledgment

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115736, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.
• STEP 1 – Recognize the extent of the problem
• STEP 2 – Understand disease before dementia
• STEP 3 – Characterize an individual’s risk
• STEP 4 – Personal & Public Intervention
• STEP 1 – Recognize the extent of the problem DONE

• STEP 2 – Understand disease before dementia DOING

• STEP 3 – Characterize an individual’s risk SOON

• STEP 4 – Personal (NO) & Public Intervention NOW?