Contemporary populations and dementia, what have we learnt and where are we headed?

Carol Brayne
Director
Cambridge Institute of Public Health

Hobart, Australia, June 2019

UNIVERSITY OF CAMBRIDGE

Framework (Public Health)

- What is the condition and its context (within us and within societies)
- Is there any evidence of change
- What does this mean

The role of population studies to provide evidence

- Working on areas of importance to society
- Describing disorders/states which are identified as key
- What, who, when, where and why
- Empirical evidence with known denominator
- The meaning of the disorder/state for societies, groups and times
- Relationship to other factors – risk/protection, lifecourse, natural history
- Testing changes in diagnostic boundaries
- Testing changes across time
- Key evidence for all types of prevention

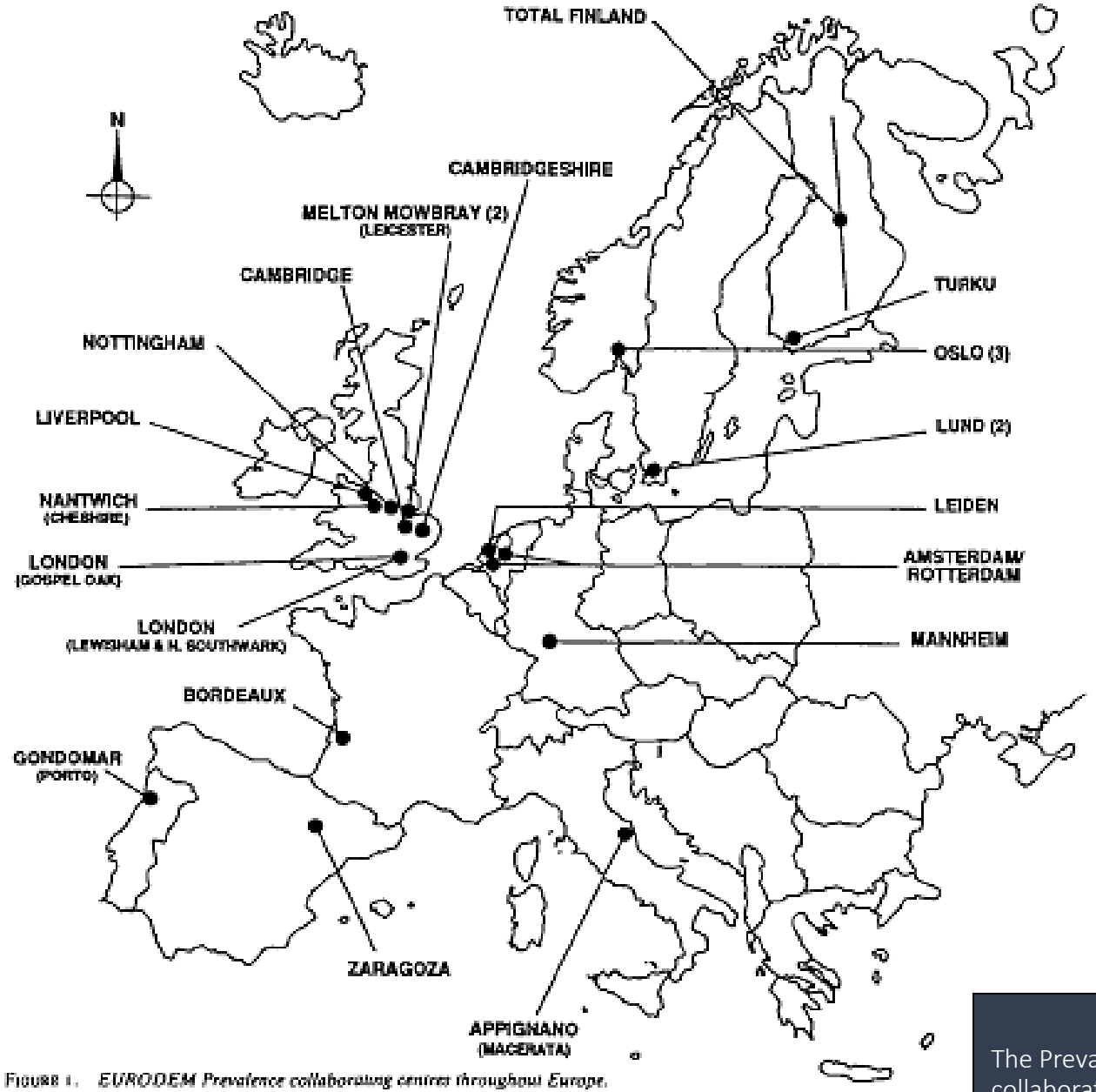
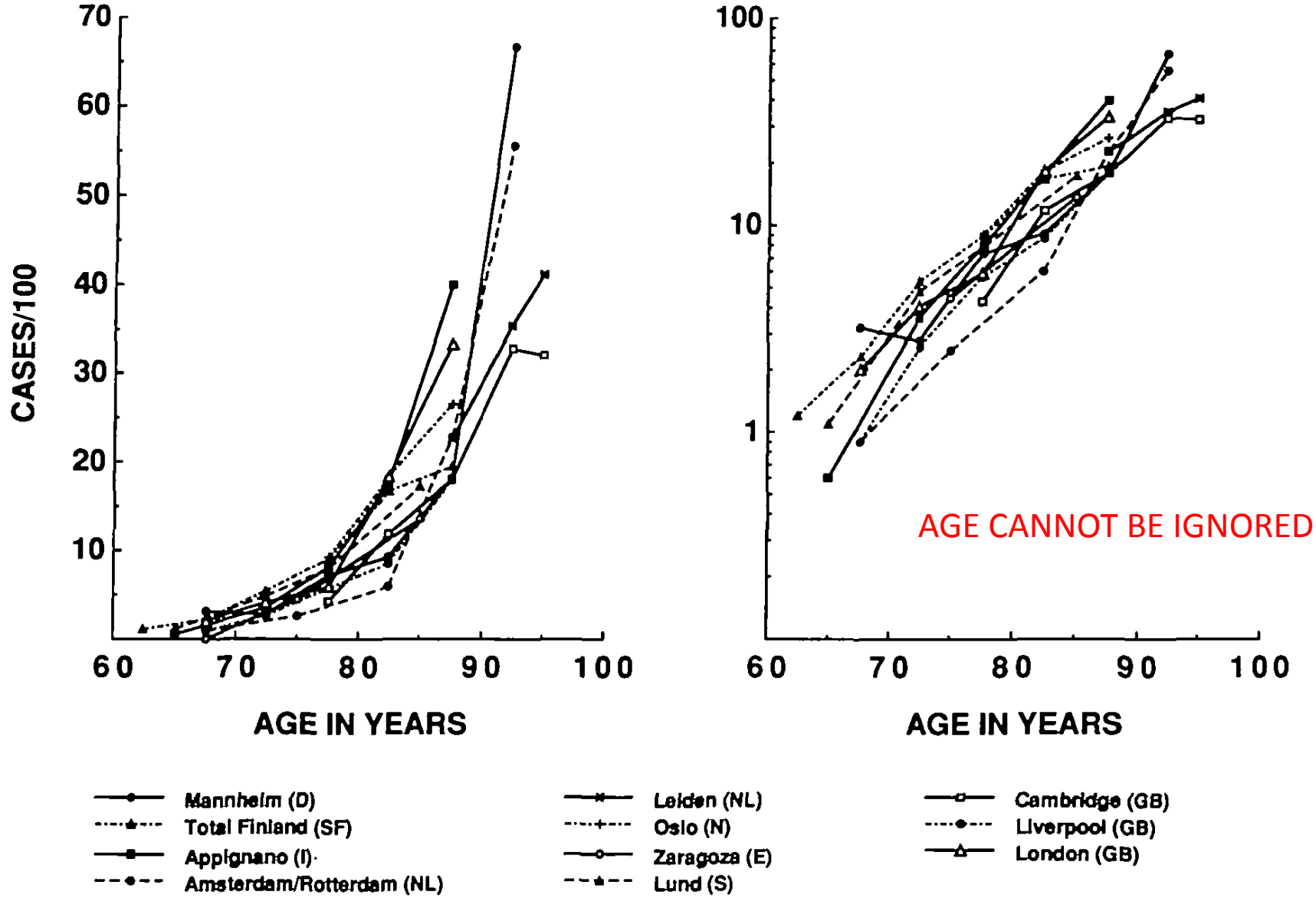


FIGURE 1. *EURODEM Prevalence collaborating centres throughout Europe.*

Creating the population evidence base
EURODEM 1990s
(Hofman, Rocca et al)

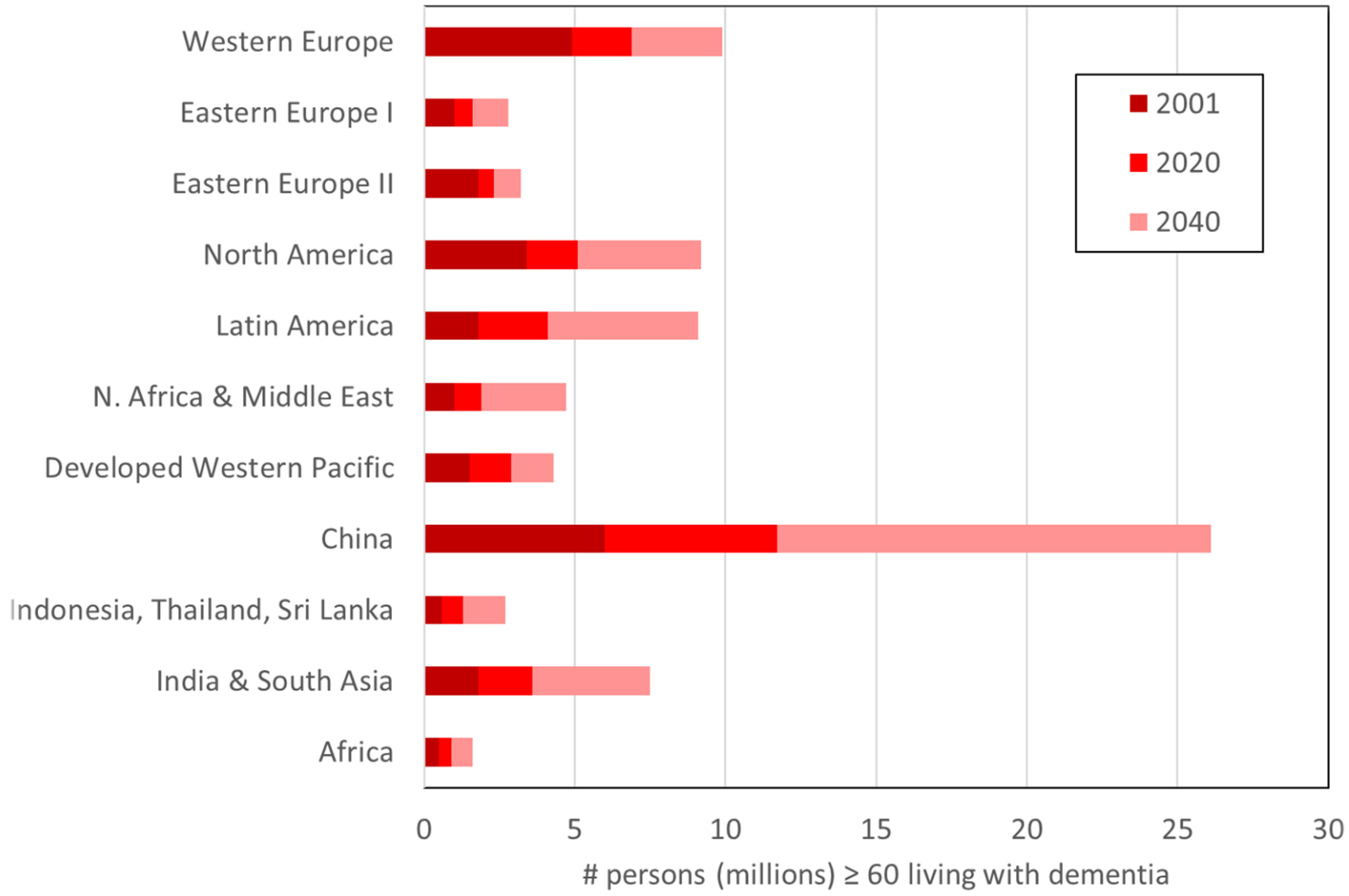
Important for bringing dementia to world awareness

The Prevalence of Dementia in Europe: a collaborative study of 1980-l990 findings. Int J of Epidemiol 1991, 20(3), 736-48.



Hofman et al Int J Epi 1991

Global prevalence of dementia



Lancet 2005;366:2112-17

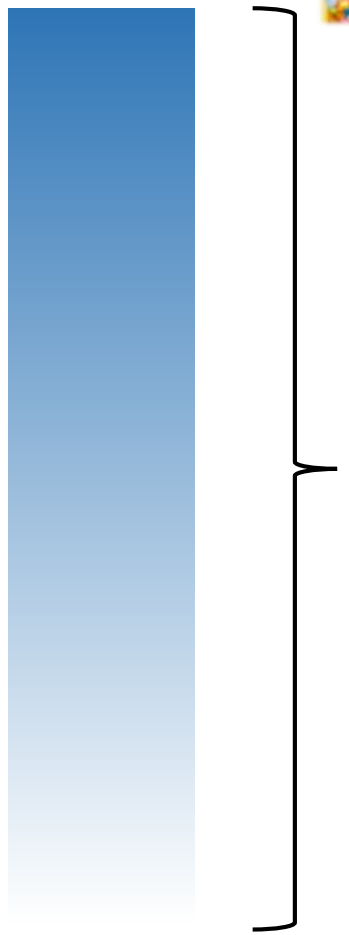
Dementia syndrome itself *

- Cognitive function
- Functional ability
- Physical health
- Mental health
- Consciousness

Clinical dementia syndrome

Impairment but not meeting Clinical dementia syndrome criteria

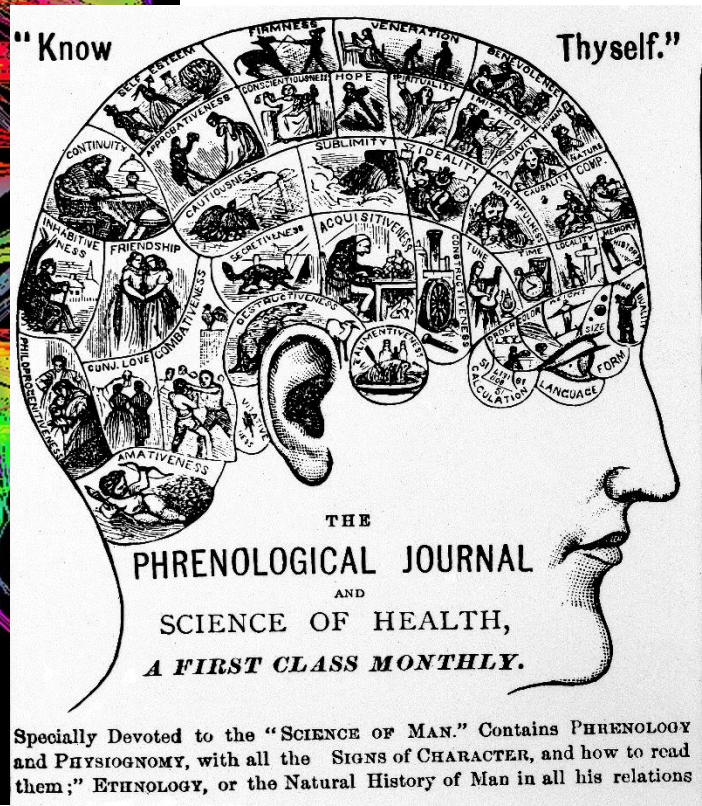
Not meeting either of the above



None are binary

*‘225,000 will develop dementia this year, that’s one every three minutes’ taken from Alzheimer’s Society, UK June 2019

Imaging, -omics, data science, history and fashions



Different research results from different research settings as different people land up in different types of services

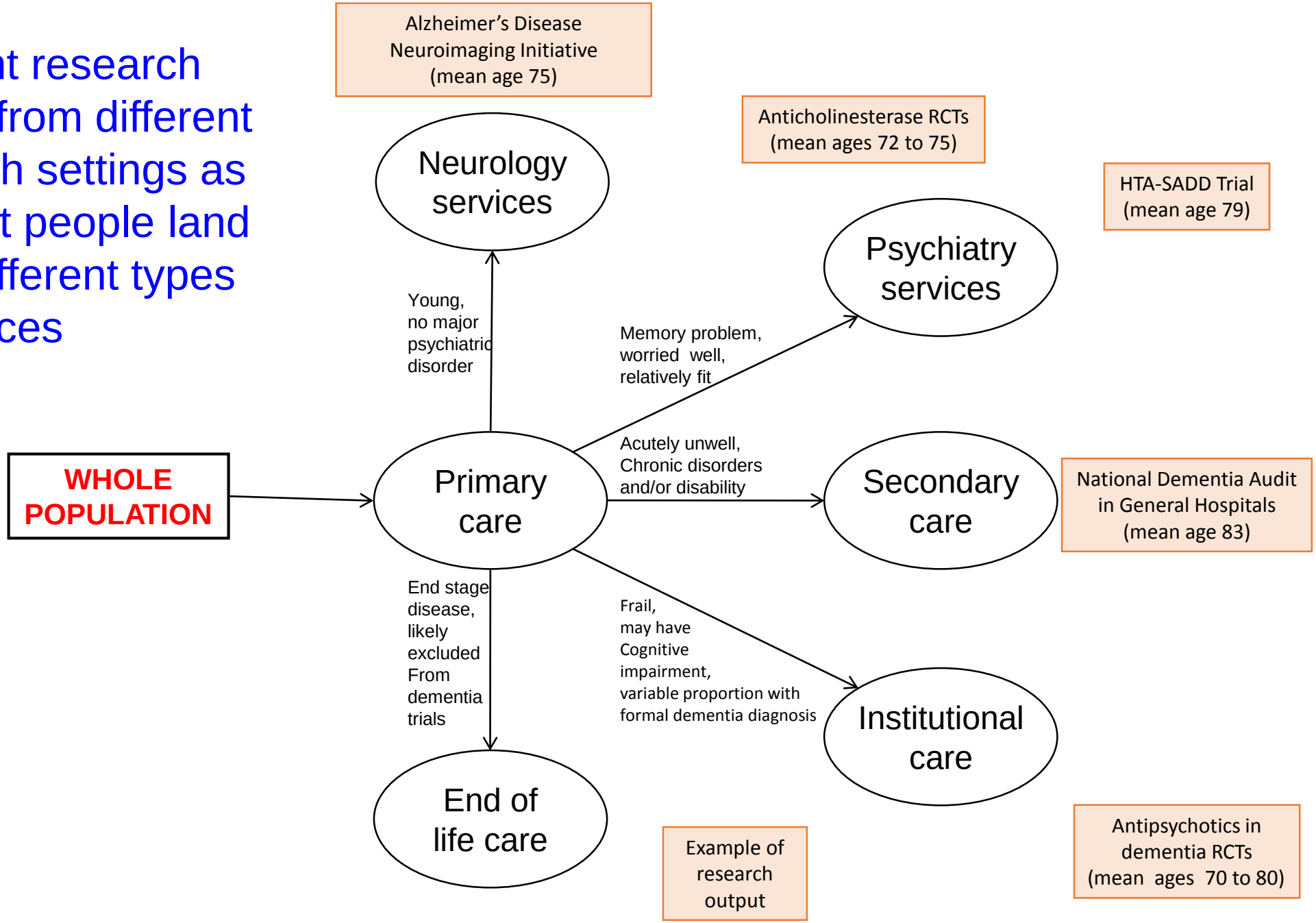
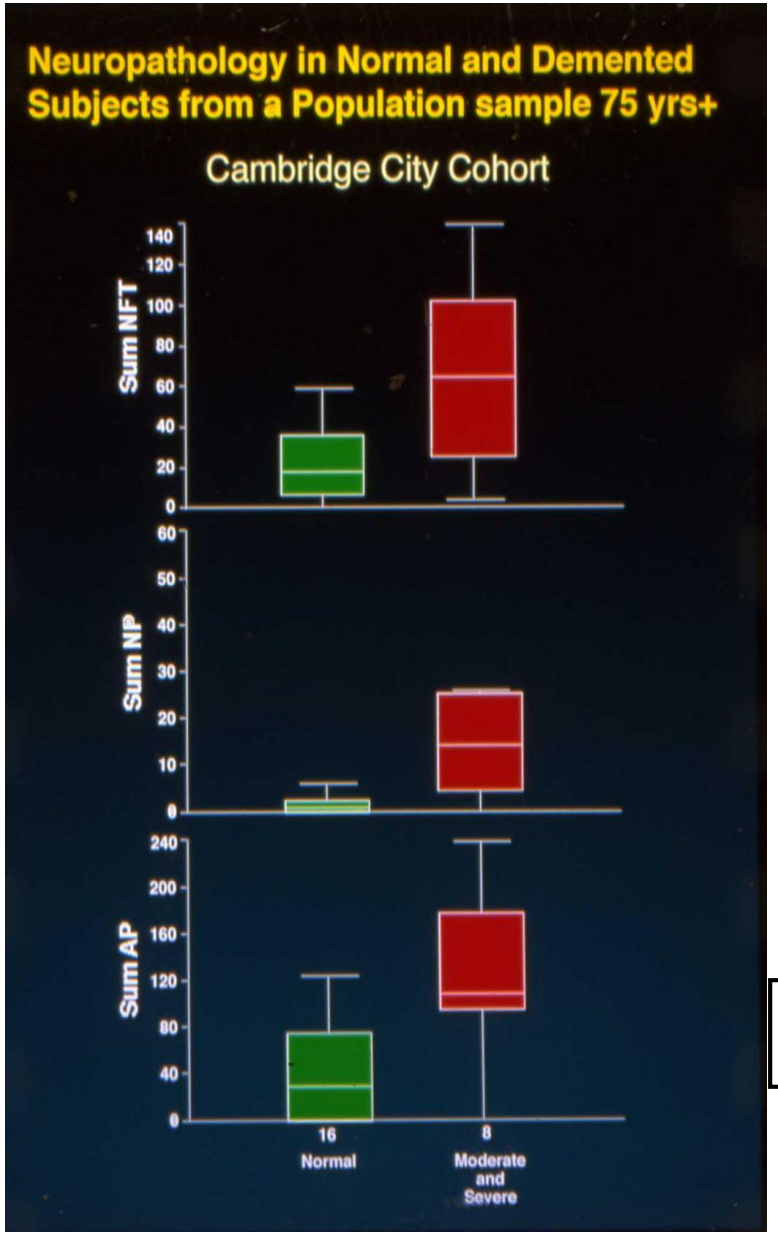
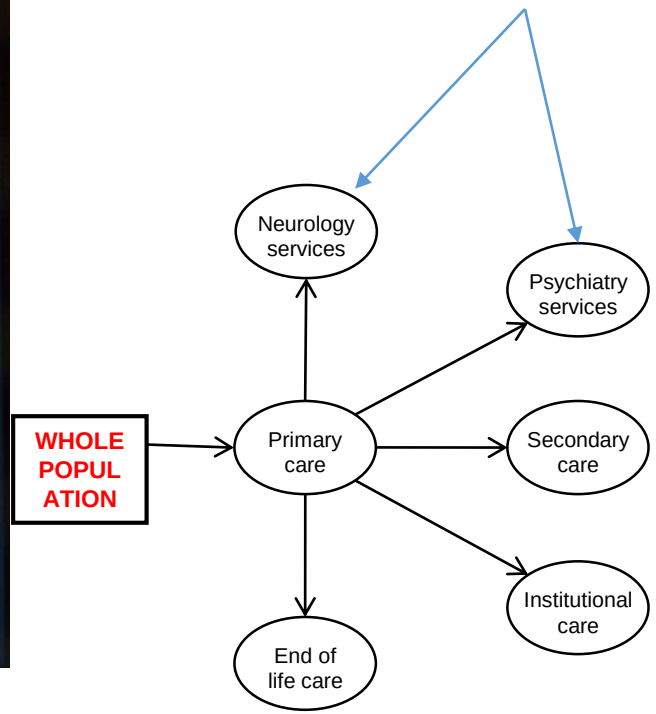
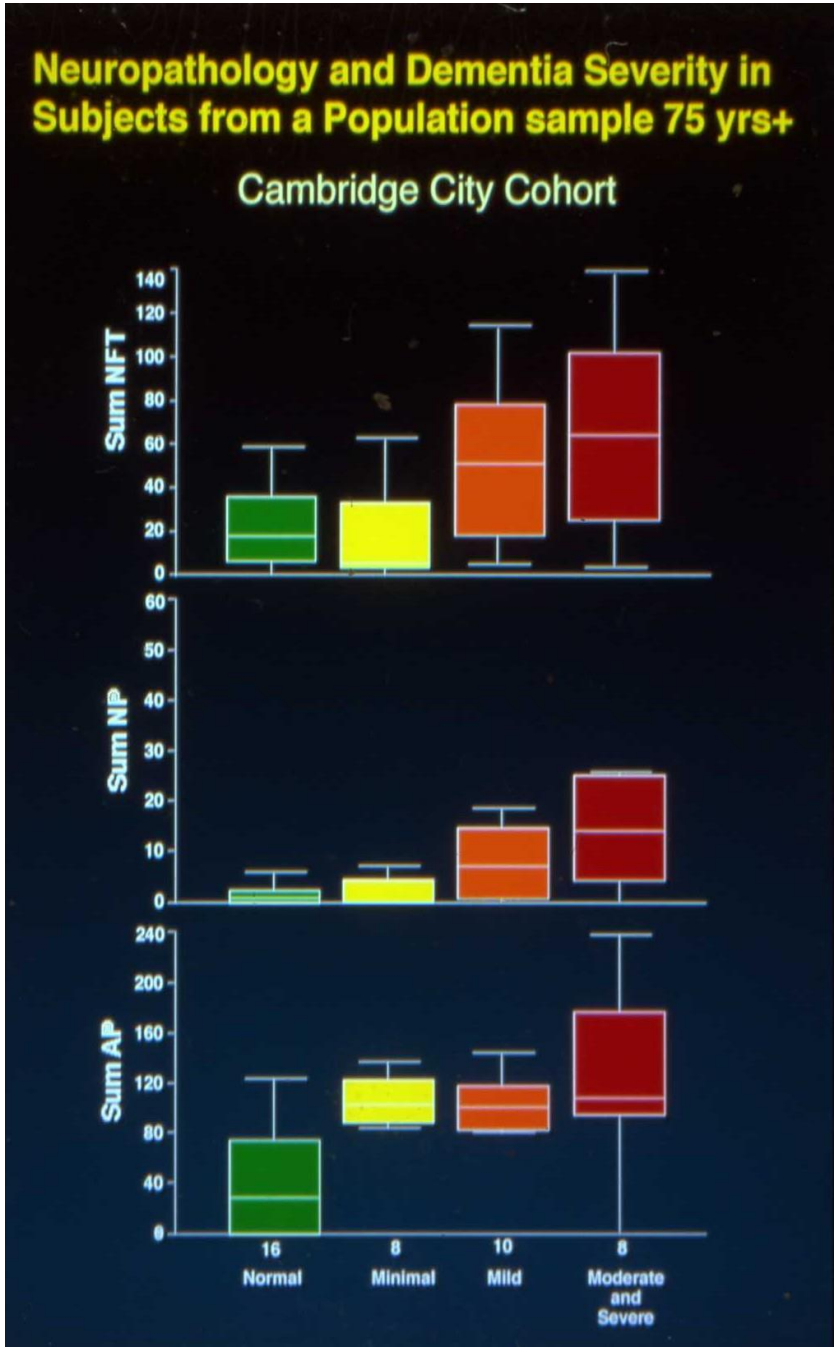
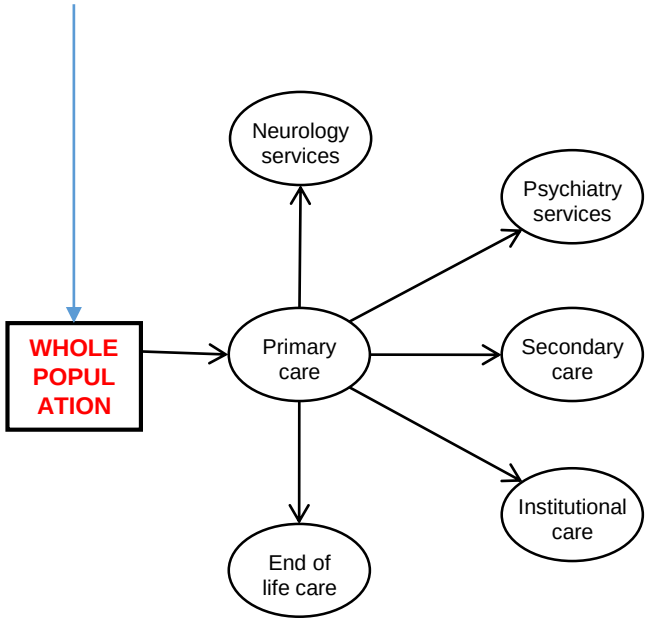


Illustration of the partial picture if we don't study the population (communication at Lancet conference, Edinburgh, 1996)





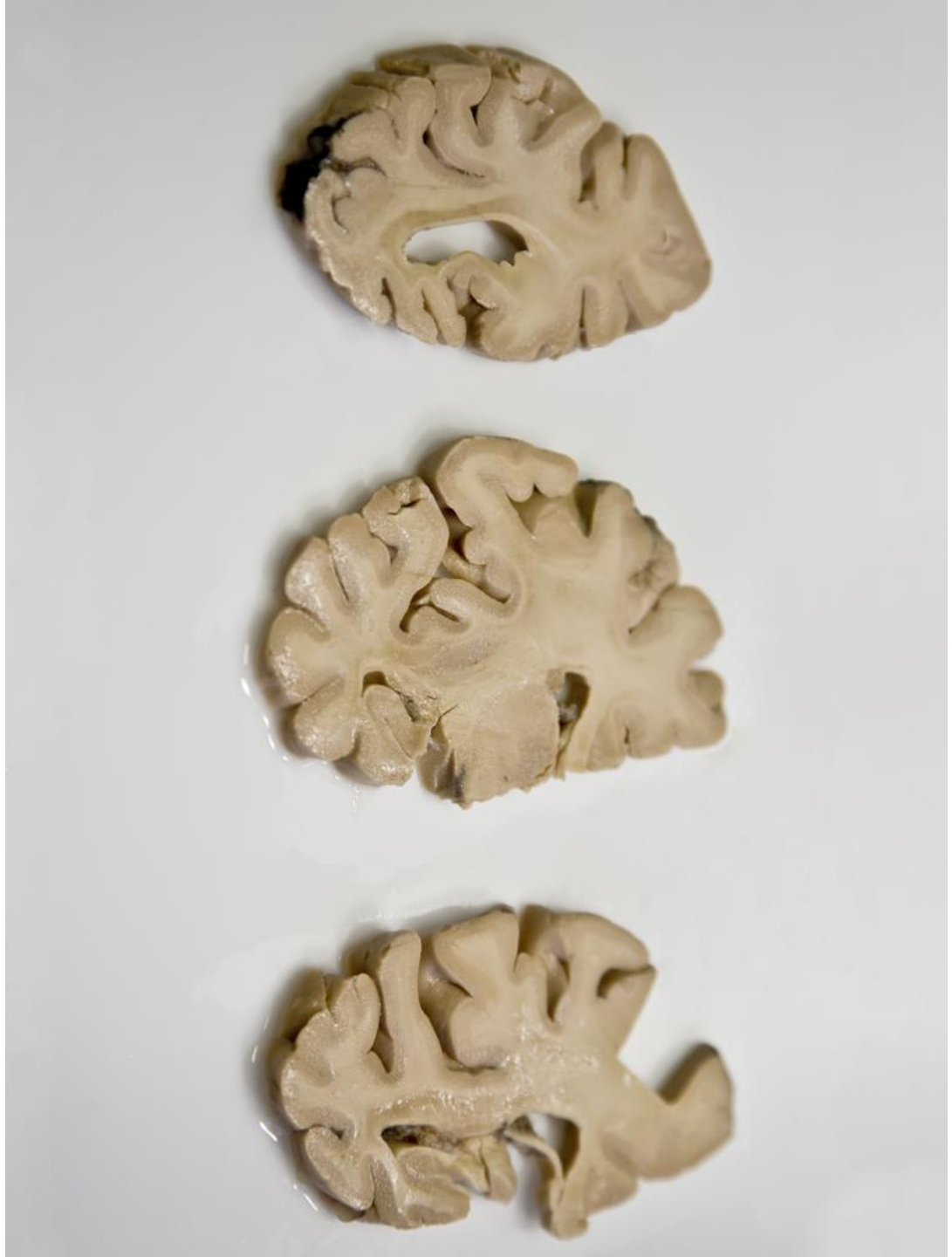

Neuropathology and Dementia Severity in Subjects from a Population sample 75 yrs+
Cambridge City Cohort
Sum NFT
140
120
100
80
60
40
20
0
Sum NP
60
50
40
30
20
10
0
Sum AP
240
200
160
120
80
40
0
16
Normal
8
Minimal
10
Mild
8
Moderate and Severe


WHOLE POPUL ATION
Primary care
Neurology services
Psychiatry services
Secondary care
Institutional care
End of life care

One national study:
The UK's Cognitive Function and Ageing Studies

Brief design of original CFAS (MRC/DH funded)

- 18,304 individuals recruited 1989-93
- 65+ population sampling equal weight <75,75+
- 5 identical centres, 1 non identical centre
- True populations – institutions included
- ~ 80% response rate at each stage
- Subsets followed at varying intervals – all at 2 and 10 years
- Detailed interviews to capture data relevant to differential diagnosis of mental health disorders in later life (GMS and CAMDEX) with algorithic diagnosis of dementia status (DSM-IIIR equivalent)
- Bioresource & brain donation (>500 brains)



MIND OVER MATTER

BRONWYN PARRY ANIA DABROWSKA

www.mindovermatterproject.co.uk

Supported by wellcome trust Queen Mary University of London UNIVERSITY OF CAMBRIDGE

Epidemiological Neuropathology
Attributable risks for dementia at death (CFAS)

- 456 donations
- AR – estimate of relative contributions of specific pathologies to dementia at death

Table 1 from Journal of Alzheimer's Disease 25 (2011) 359–372

Table 1

Population attributable risk for the main contributors to dementia in the population, based on 456 donations to MRC CFAS.

Category	Thresholds for variables within each category	Population Attributable Risk (PAR) %	Total PAR for category %
Age	80–89 y	8	
	≥ 90 y	10	18
Brain weight	Average	5	
	Low	12	17
Alzheimer's disease	Severe neuritic plaques	8	
	Moderate or severe neurofibrillary tangles	11	19
Vascular pathology	Multiple vascular pathologies (generally small vessel disease and infarction)	9	
	Small vessel disease	12	21
	Cerebral Amyloid Angiopathy[†]	*10*	–
Other pathologies	Lewy bodies	3	
	Hippocampal atrophy	12	15

[†]Cerebral amyloid angiopathy has not been included in the total for any category because it encompasses elements both of vascular and Alzheimer's disease pathology.

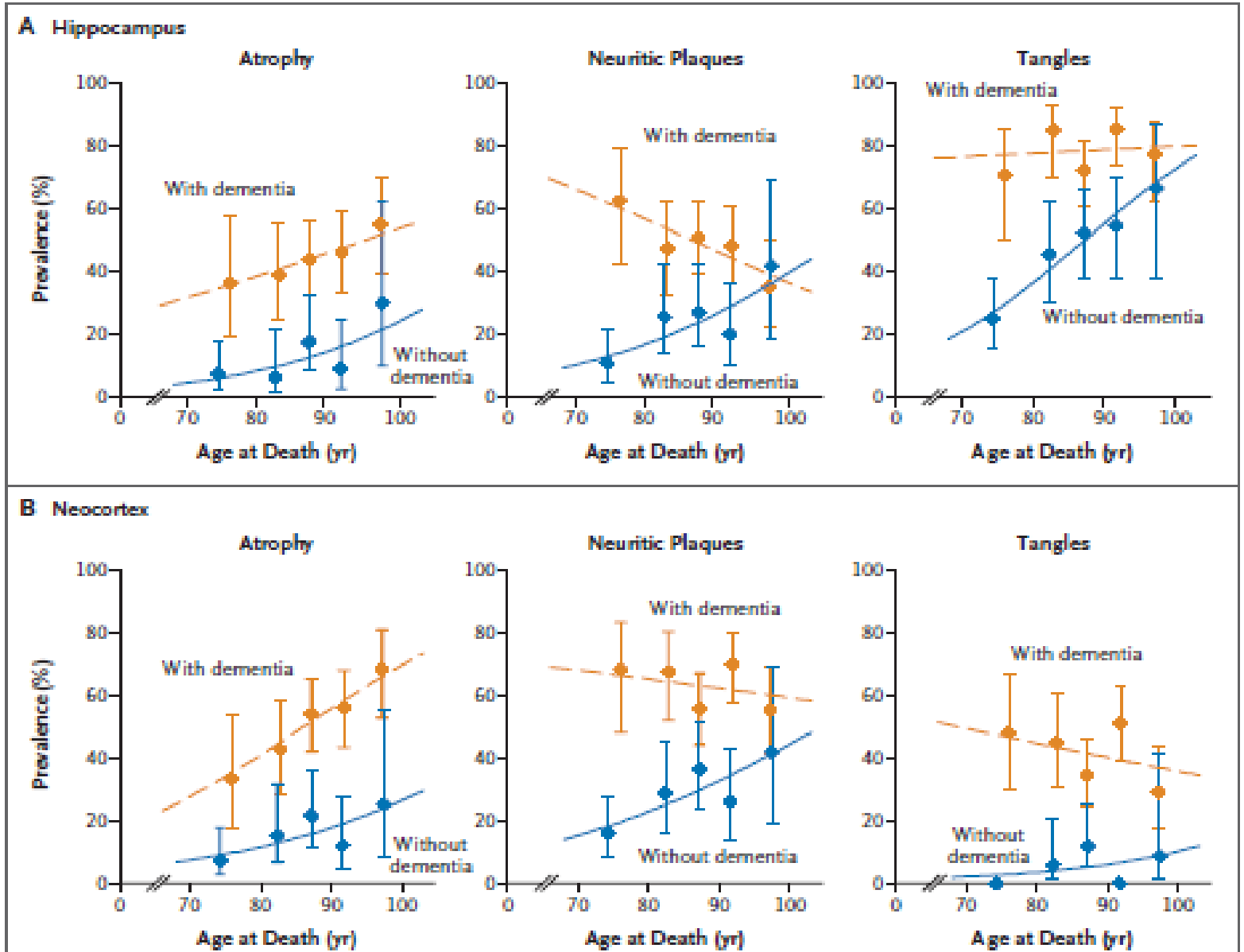


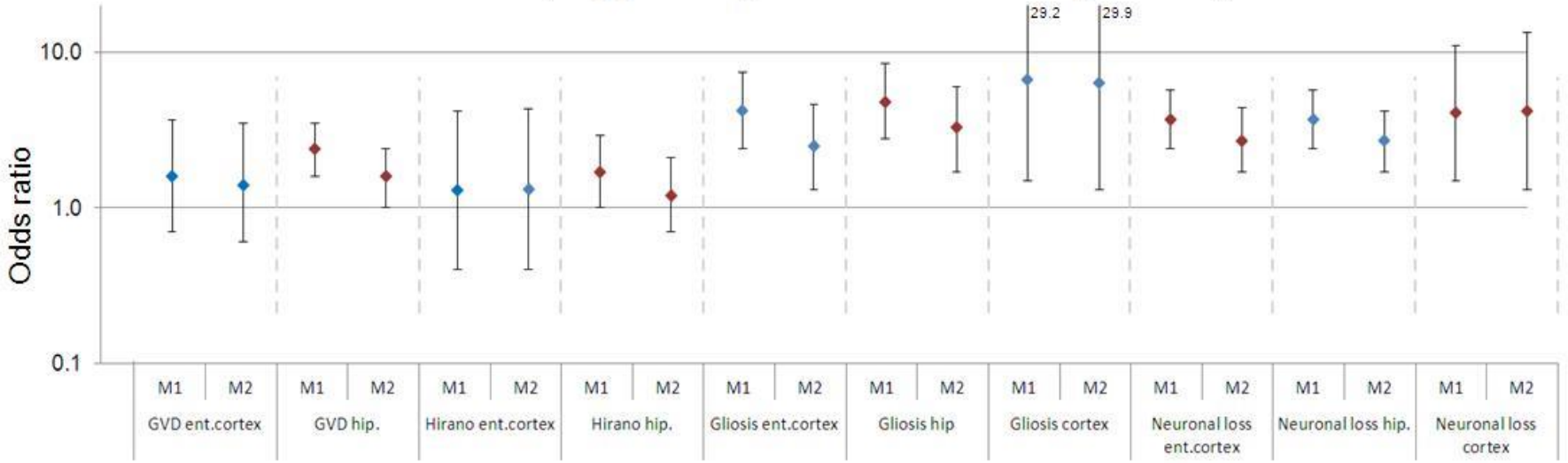
Figure 1. **Modeled and Observed Prevalence of Moderate or Severe Pathological Lesions According to Age.**
Persons who died with dementia (yellow) are compared with those who died without dementia (blue). Filled symbols represent the observed prevalence of moderate or severe pathological lesions, and I bars show the 95% confidence intervals. The solid and broken lines represent modeled prevalence values.

Age matters: AD neuropath loses its close association with dementia in the oldest old

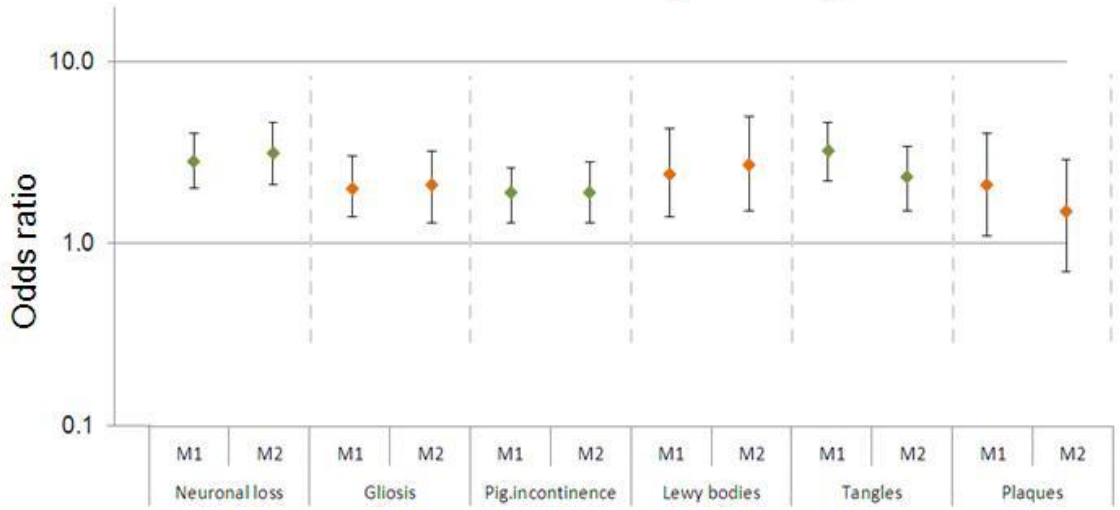
NEJM 2009; 360:2302-2309

Less common and “disregarded” pathologies in late onset dementia matter

Risk of clinical dementia: cortical, hippocampal and entorhinal pathologies



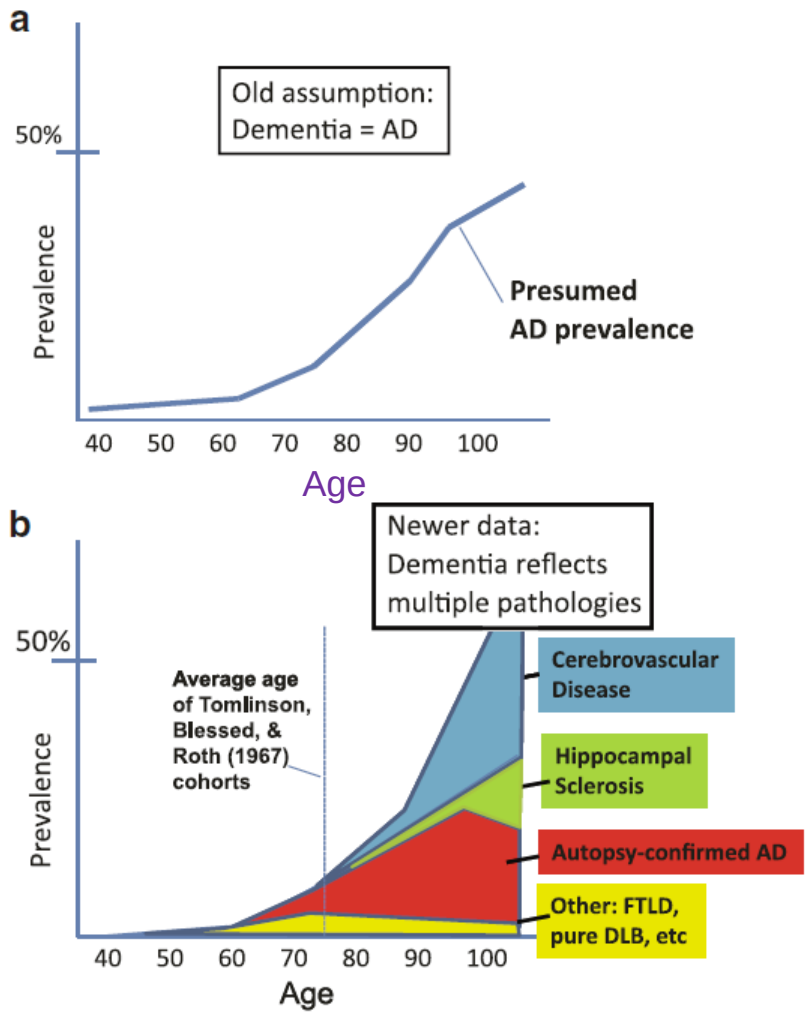
Risk of clinical dementia: brainstem pathologies



M1= adjusted for age group, study and sex

M2=adjusted for age group, study, sex, cortical neuritic plaques and Braak stage

Keage et al, JAD 2012



In advanced old age, non-AD pathologies underlie much of clinical dementia

Younger people have less complex neuropathologies

Nelson et al,
Acta Neuropathologica
2011

University of Kentucky

Adapted from slides from Peter Nelson with thanks

doi:10.1093/brain/awz099 BRAIN 2019: 0; 1–25 | 1

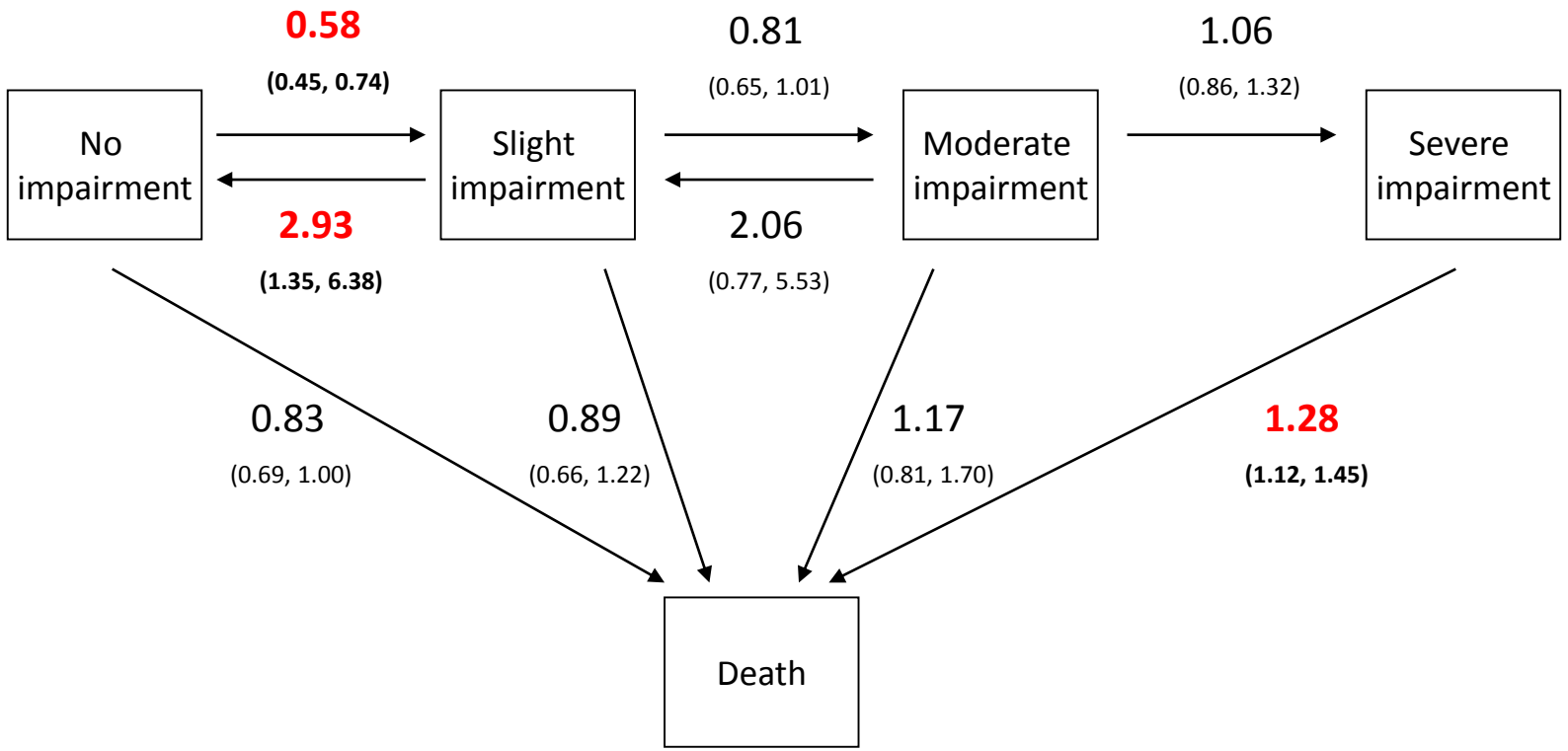
BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Peter T. Nelson,[1] Dennis W. Dickson,[2] John Q. Trojanowski,[3] Clifford R. Jack Jr.,[4] Patricia A. Boyle,[5] Konstantinos Arfanakis,[5,6] Rosa Rademakers,[2] Irina Alafuzoff,[7] Johannes Attems,[8] Carol Brayne,[9] Ian T.S. Coyle-Gilchrist,[9] Helena C. Chui,[10] David W. Fardo,[1] Margaret E. Flanagan,[11] Glenda Halliday,[12] Suvi R.K. Hokkanen,[9] Sally Hunter,[9] Gregory A. Jicha,[1] Yuriko Katsumata,[1] Claudia H. Kawas,[13] C. Dirk Keene,[14] Gabor G. Kovacs,[15] Walter A. Kukull,[14] Allan I. Levey,[16] Nazanin Makkinejad,[6] Thomas J. Montine,[17] Shigeo Murayama,[18] Melissa E. Murray,[2] Sukriti Nag,[5] Robert A. Rissman,[19] William W. Seeley,[20] Reisa A. Sperling,[21] Charles L. White III,[22] Lei Yu[5] and Julie A. Schneider[5]

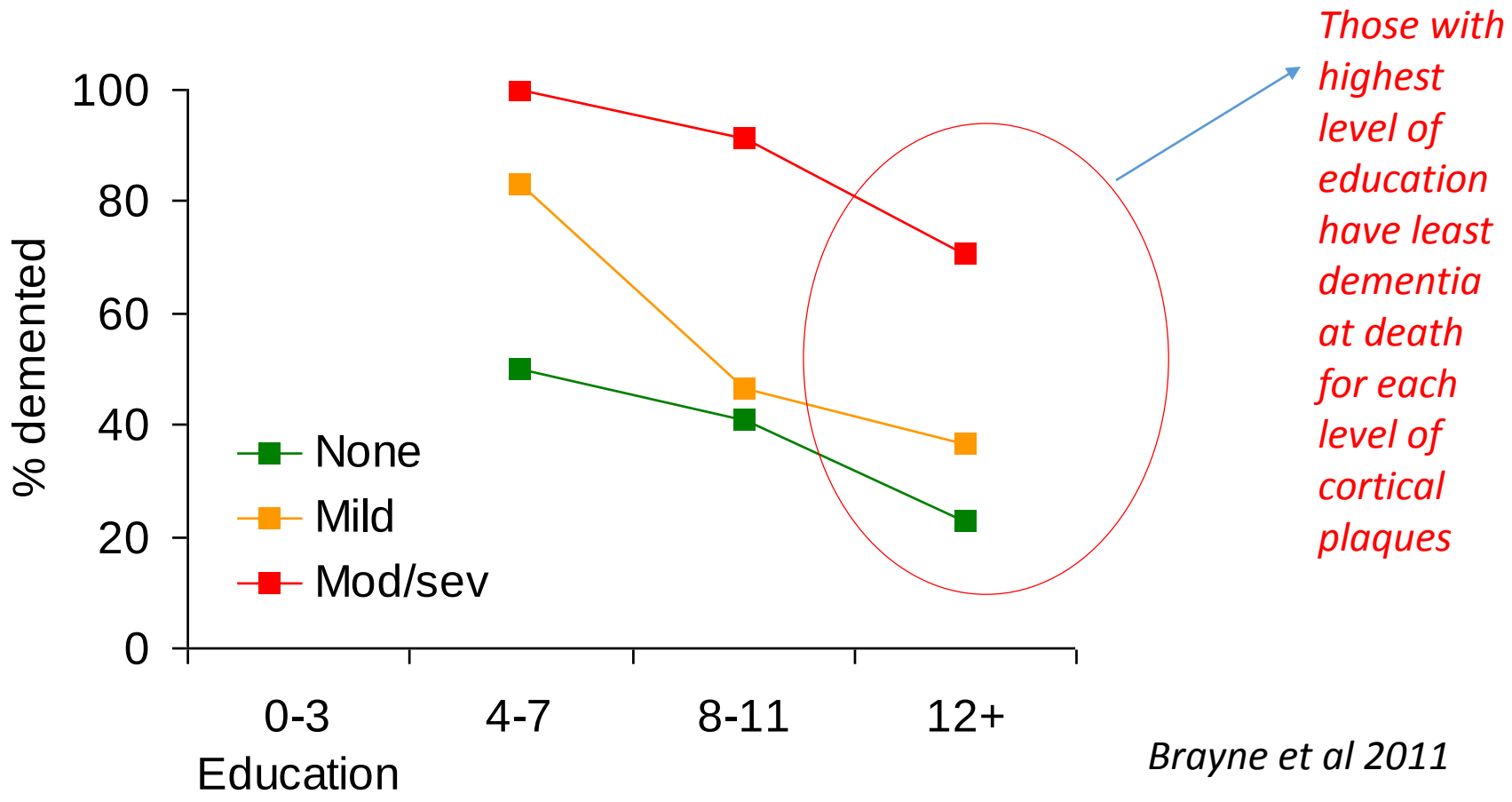
Beyond dementia: cognitive transitions are influenced by 'cognitive lifestyle' (top third v lower third)



- Combined education exposure, occupational complexity, social/intellectual engagement
- Education and occupation closely related, mostly education driven
- Later life effects independent (Marioni et al, 2011)

Influences beyond traditional neuropathologies matter: cognitive/brain reserve & compensation, empirical data

Biological mechanisms - Cortical plaques (none, mild, mod/sev), education levels and expression of dementia from ECliPSE,

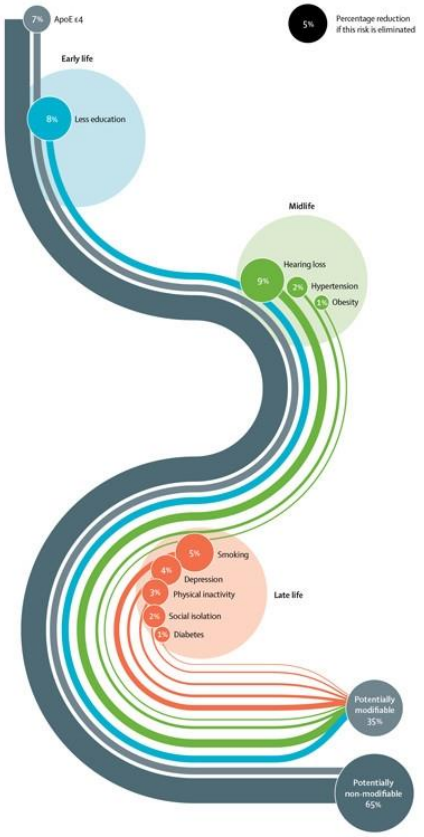


Brayne et al 2011

Synthesis of risk data- modelling prevention potential

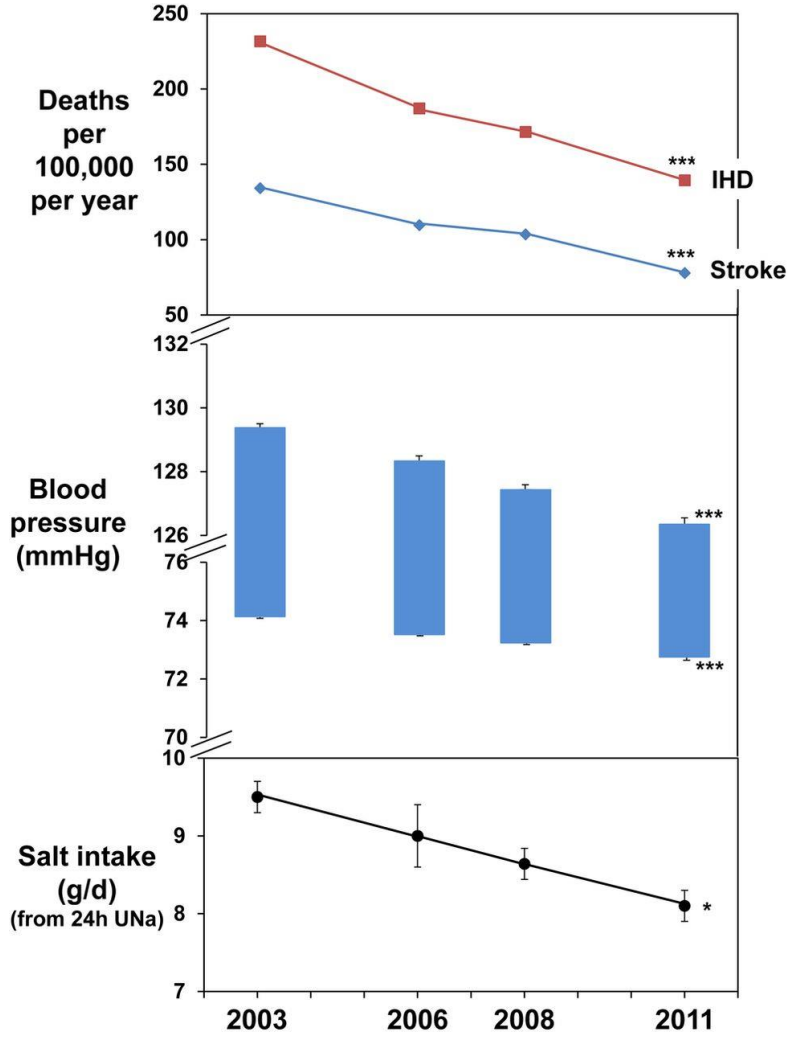
Seven risk factors emerged from cohort studies

- Potential proportion of dementia (AD) in the population that might be attributed to seven risk factors (with assumptions)
- 30% attributable to
  - diabetes,
  - midlife hypertension,
  - midlife obesity,
  - physical inactivity,
  - depression,
  - smoking,
  - low educational attainment
  - *taking into account the important inter-relationships between these variables*



(Norton et al, Lancet Neurol 2014, method adopted by Lancet Commission with addition of 2 further risk factors, 2017)

Dramatic changes in cardiovascular disease and risk factors in populations

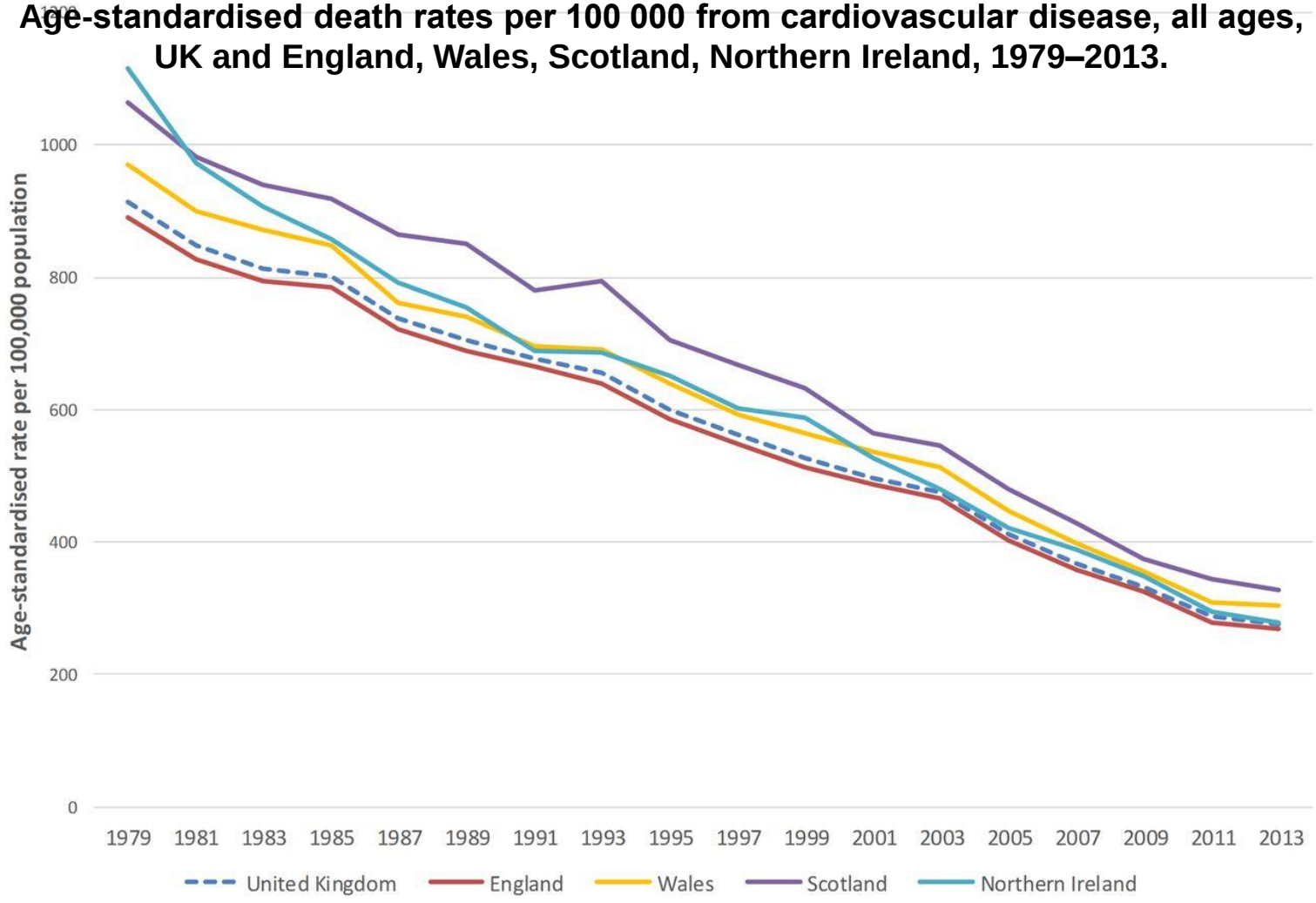


Feng J He et al. BMJ Open 2014;4:e004549

©2014 by British Medical Journal Publishing Group

BMJ Open

Age-standardised death rates per 100 000 from cardiovascular disease, all ages, UK and England, Wales, Scotland, Northern Ireland, 1979–2013.



Prachi Bhatnagar et al. Heart 2016;102:1945-1952

Heart

Evidence of change: CFAS II

CFAS II

Cognitive Function & Ageing Study

- CFAS I (1989 – 1994)
  - n = 5,156
- CFAS II (2008 – 2011)
  - n = 5,288

nature COMMUNICATIONS

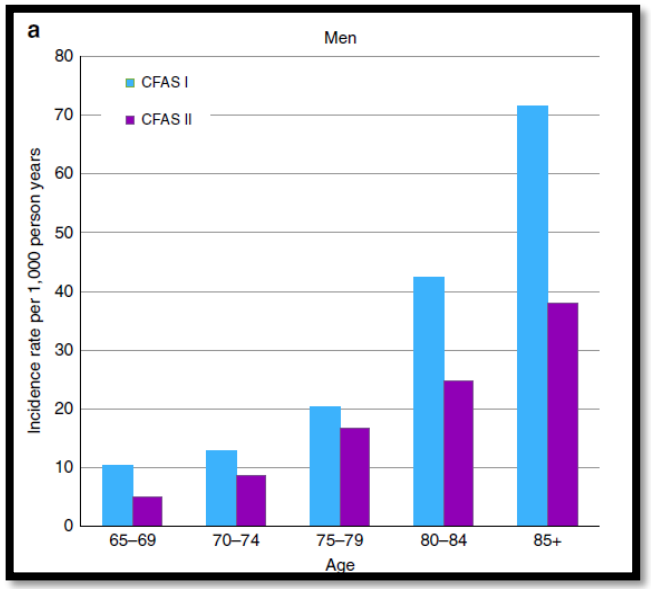
ARTICLE

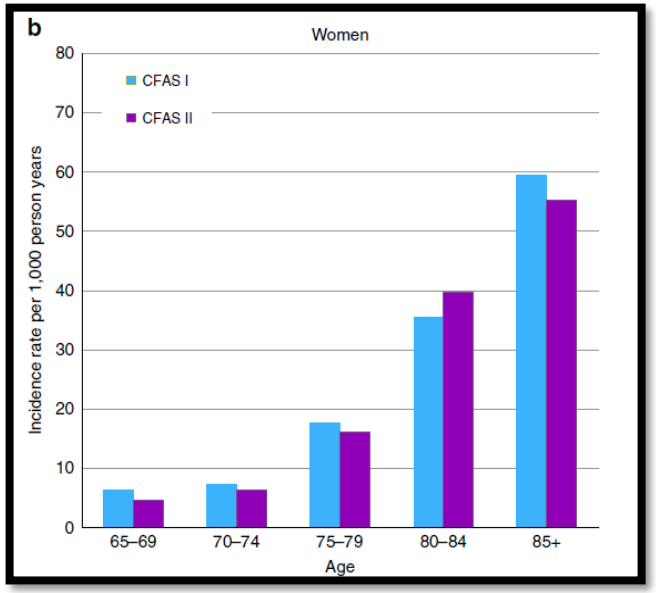
Received 30 Sep 2015 | Accepted 21 Mar 2016 | Published 19 Apr 2016

DOI: 10.1038/ncomms11398 OPEN

A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II

F.E. Matthews[1,2], B.C.M. Stephan[2], L. Robinson[2], C. Jagger[2], L.E. Barnes[3], A. Arthur[4], & C. Brayne[3], Cognitive Function and Ageing Studies (CFAS) Collaboration[#]





Incidence of dementia ↓20% driven by men's decline

CFAS
Cognitive Function & Ageing Study

Alzheimer Cohorts Consortium

- 9 prospective, population cohorts
  - Population-based
  - Prospectively collected
  - A sample size of at least 3,000 at baseline
  - Similar methods of assessment of dementia

    - Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study
    - Atherosclerosis Risk in Communities (ARIC) study
    - Cardiovascular Health Study (CHS)
    - Cognitive Function and Ageing Studies (CFAS)
    - Framingham Heart Study (FHS)
    - Gothenburg population studies
    - Personnes Agées QUID (PAQUID) study
    - Rotterdam Study
    - Three-City Study (3C)

Total: 59,230 individuals; 343,248 person-years

- Incidence Rates (IR) over period of 5 years
  - All data from 1988 through 2015
  - Stratified by age group & sex

- Trends in Incidence
  - Over 25 years (1990 – 2015)
  - All-cause dementia
  - Alzheimer's Disease
  - Stratified by sex

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

With thanks to L. Chibnik for ACC slides

Dementia now: multi-morbidity in different living situations (CFAS II)

Long term care settings		CFAS I			CFAS II		
		n	%	95% CI	n	%	95% CI
Number of health conditions	0	63	18.5	14.7 – 23.0	11	5.5	2.9 – 10.1
(not including dementia)	1	53	15.9	12.3 – 20.2	25	13.2	8.7 – 19.6
	2	60	18.1	14.3 – 22.6	33	18.5	12.9 – 25.9
	≥3	158	**47.6**	42.3 – 53.1	119	**62.7**	54.8 – 70.0

Assisted living facilities		CFAS I			CFAS II		
		n	%	95% CI	n	%	95% CI
Number of health conditions	0	52	7.5	5.7 – 9.7	13	2.9	1.7 – 5.1
(not including dementia)	1	126	18.5	15.7 – 21.6	50	10.1	7.7 – 13.1
	2	149	22.0	19.0 – 25.3	72	15.1	12.1 – 18.7
	≥3	356	**52.1**	48.3 – 55.8	335	**71.9**	67.6 – 75.8

Living in the community		CFAS I			CFAS II		
		n	%	95% CI	n	%	95% CI
Number of health conditions	0	724	10.9	10.2 – 11.7	492	6.8	6.3 – 7.5
(not including dementia)	1	1481	22.4	21.4 – 23.4	1107	15.5	14.6 – 16.3
	2	1507	22.9	21.9 – 23.9	1512	21.3	20.4 – 22.3
	≥3	2885	**43.9**	42.7 – 45.1	3904	**56.4**	55.2 – 57.5

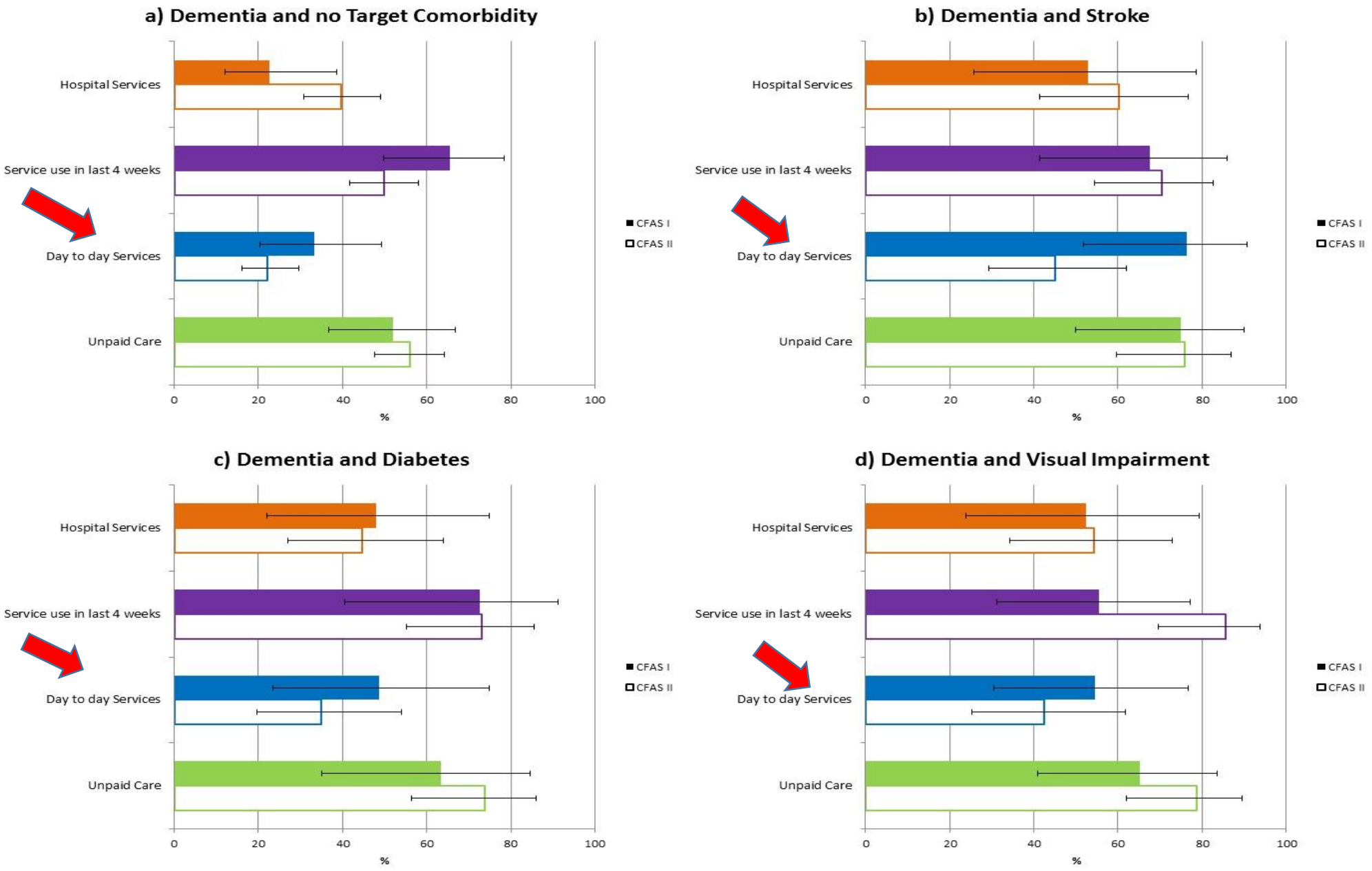
- Proportion with multi-morbidity (≥3 health conditions) increased (from 44-52% to 56-72%) between CFAS I and CFAS II
- Proportion with no additional reported health conditions dropped in all settings
- Key implications for design of services

CFAS
Cognitive Function & Ageing Study

Matthews FE, Bennett H, Wittenberg R, Jagger C, Dening T, Brayne C. 2016. PLOS ONE

Patterns of change in services in CFAS I and CFAS II

CFAS
Cognitive Function & Ageing Study



Any comorbidity is associated with increased contact with services

For all people day to day services were less likely to be reported in CFAS II

Bennett et al. (2018) BMC Medicine

HATICE

preDIVA
FINGER
MAPT

Healthy Ageing Through Internet Counselling in the Elderly

From observation to testing intervention

Aim

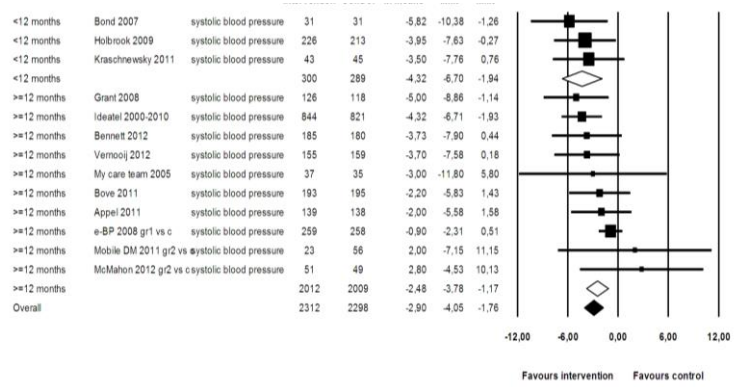
Improve vascular risk factor management to prevent cardiovascular disease, cognitive decline and dementia using an interactive internet intervention

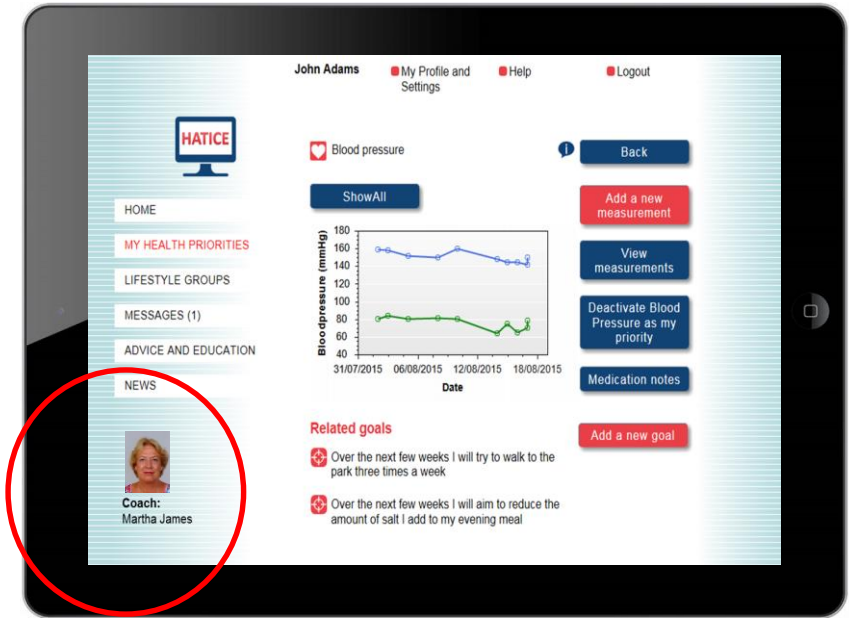
SEVENTH FRAMEWORK PROGRAMME

www.hatice.eu

Interactive internet intervention, volunteer studies and now embedded in cohorts

Focus groups:
- target population
- nurses
- doctors





- simple
- self-management
- goal-setting
- personalised
- interactive
- coach

EUROPEAN SOCIETY OF CARDIOLOGY

& now Prodemos using mobile apps

Research investment and a Research roadmap to deliver change for people affected by dementia by 2025

‘WHAT RESEARCH, IN ADDITION TO SEARCHING FOR NEW TREATMENTS, IS REQUIRED TO IMPROVE THE LIVES OF PEOPLE AFFECTED BY DEMENTIA TODAY, AND REDUCE THE RISK OF DEMENTIA FOR FUTURE POPULATIONS?’

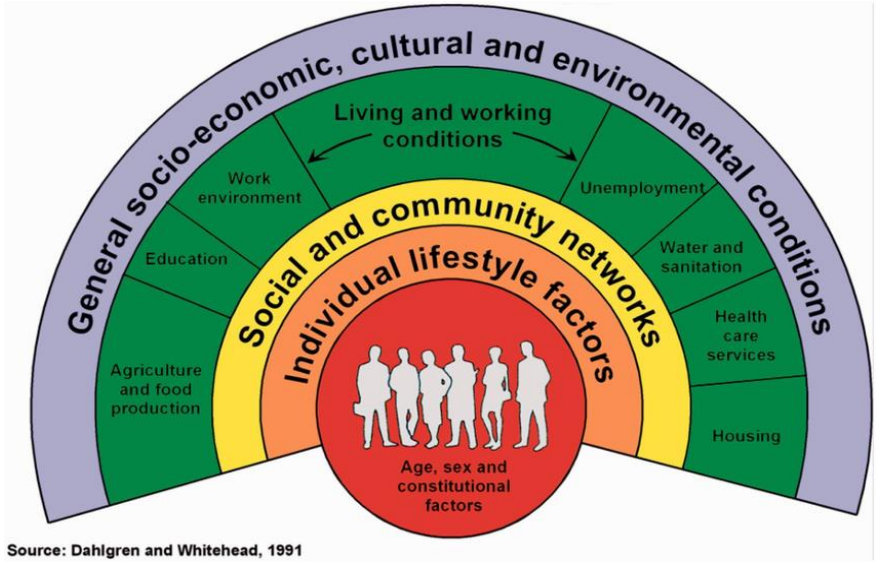
Dr James Pickett,
Head of Research, Alzheimer’s Society

@jamespickett12

Where now?

- Together we need to use such evidence to inform service and policy now & research for the future
- Clear evidence that dementia is changing in some global areas, and also our bodies and brains
- Changes across life across generations will have led to these changes
- Primary prevention at population level can address inequalities and sustainability
- Secondary and tertiary prevention research investors must take a realistic view of what the implications of current research are in the context of population evidence
- Evidence based investment….

- And co-production of healthier brains for all in our communities with embedded research to create value across the globe



Source: Dahlgren and Whitehead, 1991

CFAS Institutions and collaborations (lead collaborators)