UNIVERSITY OF CAMBRIDGE

Alzheimer's Research UK
Defeating Dementia

Cognitive reserve and life expectancy in an ageing population

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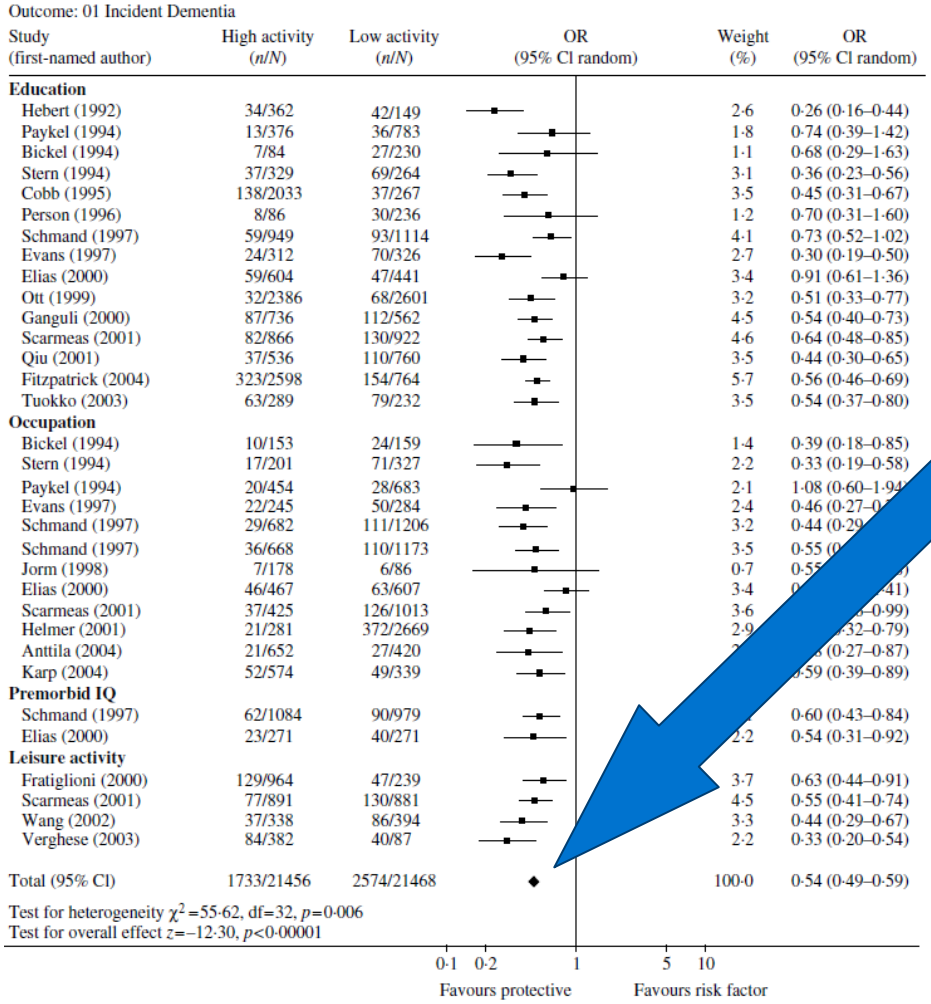
Background

- Factors associated with incident dementia and cognitive decline
  - education
  - occupational complexity
  - cognitive leisure activities

- Collectively referred to as cognitive reserve

Background



Outcome: 01 Incident Dementia

Study (first-named author)	High activity (*n*/*N*)	Low activity (*n*/*N*)	OR (95% CI random)	Weight (%)	OR (95% CI random)
Education					
Hebert (1992)	34/362	42/149		2·6	0·26 (0·16–0·44)
Paykel (1994)	13/376	36/783		1·8	0·74 (0·39–1·42)
Bickel (1994)	7/84	27/230		1·1	0·68 (0·29–1·63)
Stern (1994)	37/329	69/264		3·1	0·36 (0·23–0·56)
Cobb (1995)	138/2033	37/267		3·5	0·45 (0·31–0·67)
Person (1996)	8/86	30/236		1·2	0·70 (0·31–1·60)
Schmand (1997)	59/949	93/1114		4·1	0·73 (0·52–1·02)
Evans (1997)	24/312	70/326		2·7	0·30 (0·19–0·50)
Elias (2000)	59/604	47/441		3·4	0·91 (0·61–1·36)
Ott (1999)	32/2386	68/2601		3·2	0·51 (0·33–0·77)
Ganguli (2000)	87/736	112/562		4·5	0·54 (0·40–0·73)
Scarmeas (2001)	82/866	130/922		4·6	0·64 (0·48–0·85)
Qiu (2001)	37/536	110/760		3·5	0·44 (0·30–0·65)
Fitzpatrick (2004)	323/2598	154/764		5·7	0·56 (0·46–0·69)
Tuokko (2003)	63/289	79/232		3·5	0·54 (0·37–0·80)
Occupation					
Bickel (1994)	10/153	24/159		1·4	0·39 (0·18–0·85)
Stern (1994)	17/201	71/327		2·2	0·33 (0·19–0·58)
Paykel (1994)	20/454	28/683		2·1	1·08 (0·60–1·94
Evans (1997)	22/245	50/284		2·4	0·46 (0·27–0
Schmand (1997)	29/682	111/1206		3·2	0·44 (0·29
Schmand (1997)	36/668	110/1173		3·5	0·55 (0
Jorm (1998)	7/178	6/86		0·7	0·55
Elias (2000)	46/467	63/607		3·4	41)
Scarmeas (2001)	37/425	126/1013		3·6	–0·99)
Helmer (2001)	21/281	372/2669		2·9	·32–0·79)
Anttila (2004)	21/652	27/420			(0·27–0·87)
Karp (2004)	52/574	49/339			·59 (0·39–0·89)
Premorbid IQ					
Schmand (1997)	62/1084	90/979			0·60 (0·43–0·84)
Elias (2000)	23/271	40/271		2·2	0·54 (0·31–0·92)
Leisure activity					
Fratiglioni (2000)	129/964	47/239		3·7	0·63 (0·44–0·91)
Scarmeas (2001)	77/891	130/881		4·5	0·55 (0·41–0·74)
Wang (2002)	37/338	86/394		3·3	0·44 (0·29–0·67)
Verghese (2003)	84/382	40/87		2·2	0·33 (0·20–0·54)
Total (95% CI)	1733/21456	2574/21468		100·0	0·54 (0·49–0·59)

Test for heterogeneity χ^2=55·62, df=32, p=0·006
Test for overall effect z=–12·30, p<0·00001

0·1 0·2 1 5 10
Favours protective Favours risk factor

Cognitive reserve (education, occupation, pre-morbid IQ & leisure activity) **decreases** the risk of incident dementia by 46%

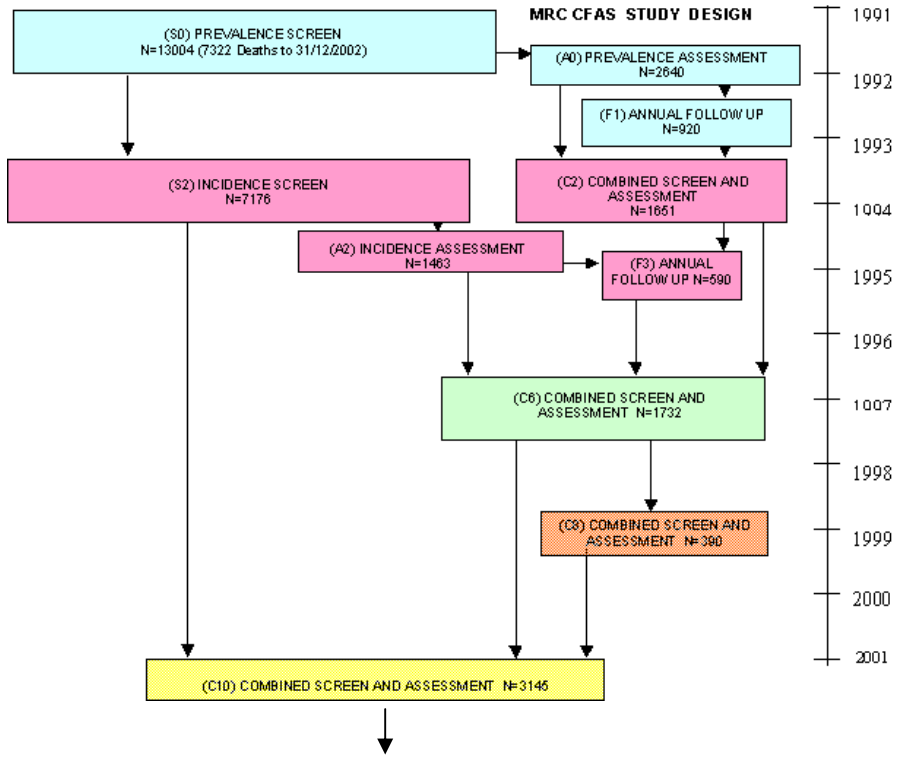
Valenzuela et al. (2006) *Psychol Med*. 36(4);441-54

Aims/Questions

- Are the different sub-components of reserve associated with
    - different cognitive trajectories from age 65?
    - different life expectancies from age 65?

MRC CFAS

- MRC Cognitive Function and Ageing Study (n = 13,004, ≥ 65 yrs, 60% F)
- Population-based across 5 urban and rural centres in England and Wales
  - Cambridgeshire
  - Gwynedd
  - Newcastle
  - Nottingham
  - Oxford
- Up to 11 assessments over 16 years
- www.cfas.ac.uk

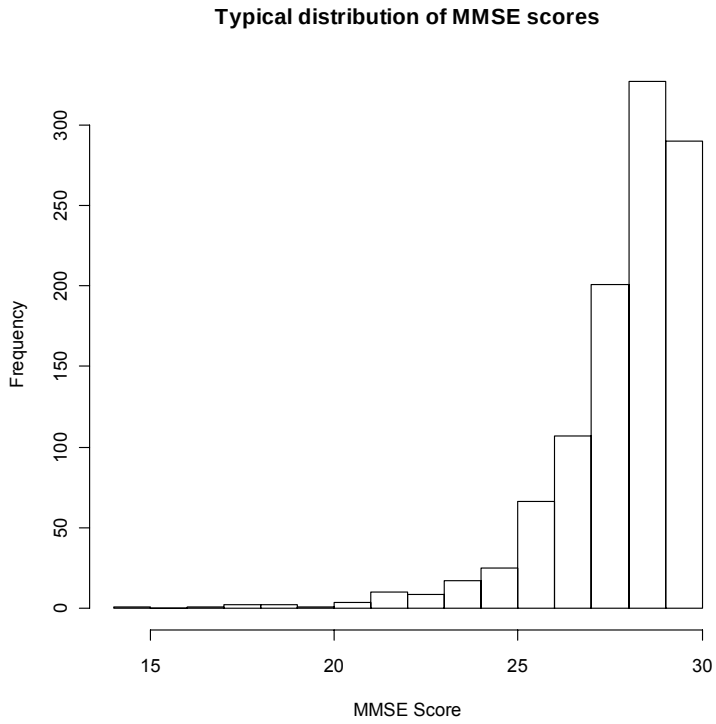


MRC CFAS – cognitive testing

- The Mini-Mental State Examination (MMSE) is widely used as a measure of global cognitive function

MMSE categories

- 0 – 22 Severe cognitive impairment
- 23 – 26 Slight cognitive impairment
- 27 – 30 No cognitive impairment



Stephan et al. (2010) *Am J Geriatr Psychiatry* 18(8):662-73.

Busse et al. (2003) *Acta Neurol Scand* 108:71-81

Cognitive reserve variables

1. **Education** level in young adulthood: self reported years of full-time education

Cognitive reserve variables

2. **Occupational complexity** in midlife

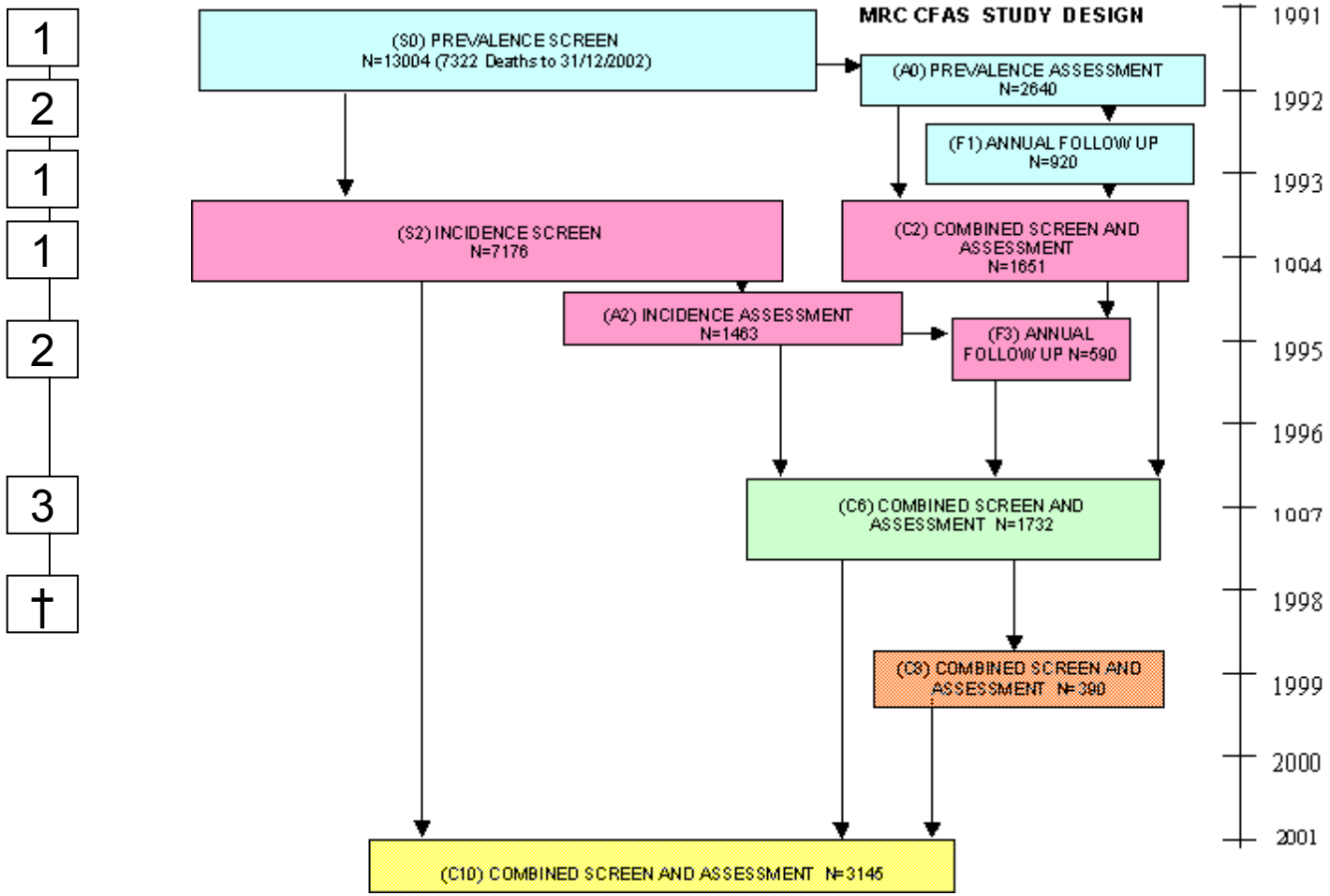
- main occupation in terms of years most worked
- recoded using two systems: social class grouping (from I to VI) and socio-economic grouping (from 11 to 150)
- no formal code for housewives – scores altered to be in the same direction as their education and current social engagement

Cognitive reserve variables

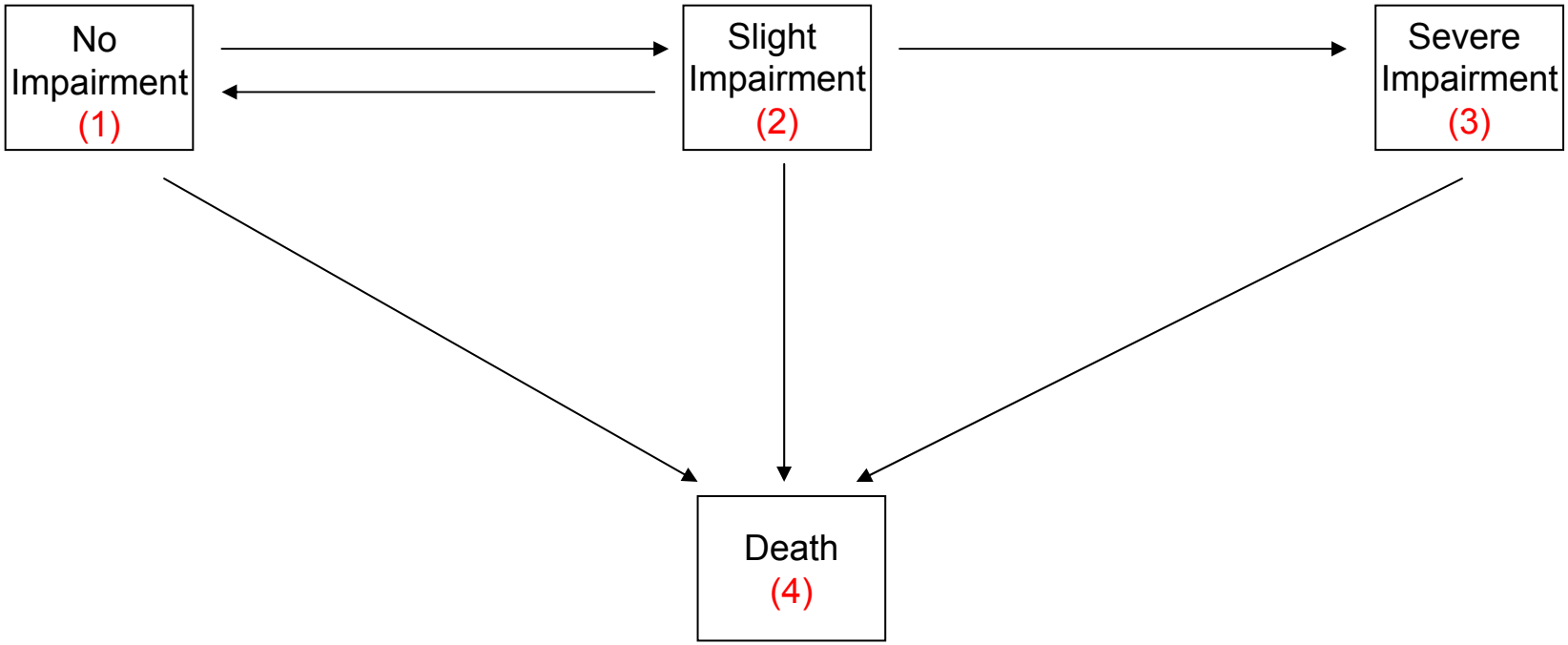
3. **Social engagement** (current levels in later life): contact with relatives and neighbours, and attending meetings

   For example, community, church or social groups, such as over 60's clubs, evening classes or other similar activities

Hypothetical cognitive trajectory



Multi-state model



Transition specific hazards: $q_{12}(t), q_{14}(t), q_{23}(t), q_{21}(t), q_{24}(t), q_{34}(t)$

Covariate effects assessed via a log linear model: $log[q_{rs}(t)] = \beta^T z(t)$

Marshall & Jones (1995) *Statistics in Medicine*, 14.

Multi-state model

- Model specification
  - misclassification (hidden Markov model)
  - absorbing state (death) and right censoring
  - time-dependent transition intensities
  - piecewise constant hazards
- Model estimated using the '*msm*' package in **R**
- Model results used to generate life expectancies

Jackson et al. (2003) *J R Stat Soc Ser D-Stat* 52(2):1-17.

Multi-state model (misclassification)

- Error in measuring MMSE
  - Observed state (X^*), true underlying state (X)
- Need to measure misclassification $\Pr(X^* = r \mid X = s)$
- Individual i could be misclassified at each measurement time-point $t_1, t_2, t_3, ..., t_m$

Covariates

- Four models (all adjust for age, sex and yr of birth –1900)
  1. Education
  2. Occupation
  3. Social engagement
  4. Education + occupation + social engagement

- All variables split into tertiles

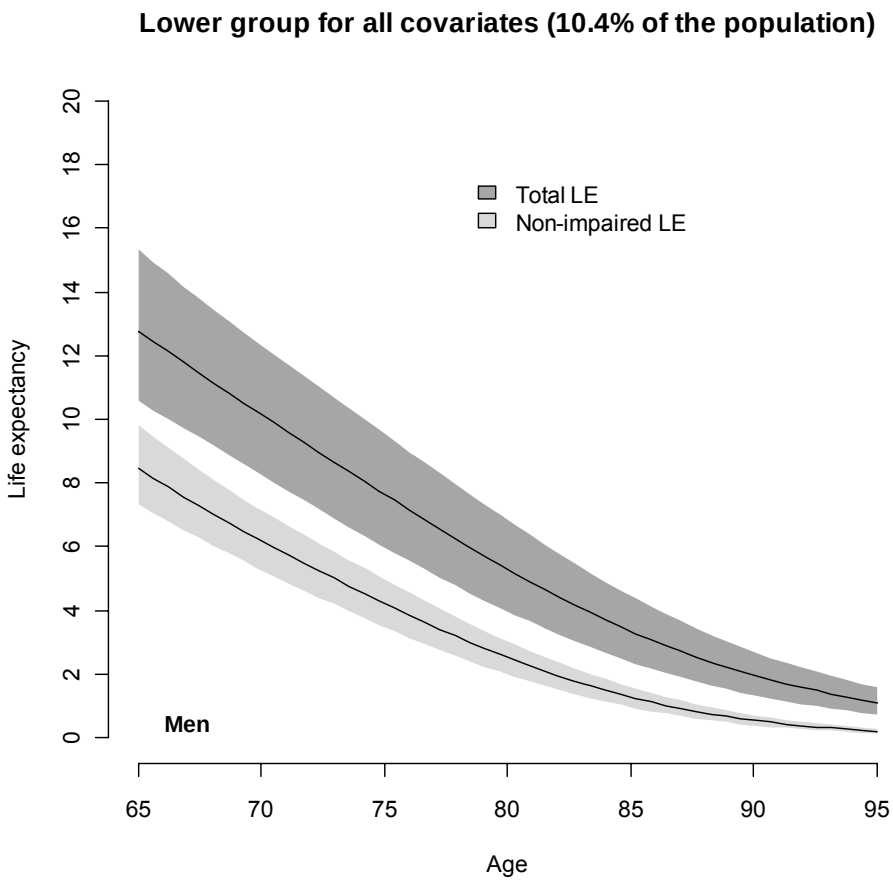
LEs by education, occupation and social engagement

- Total life expectancy is defined as the sum of occupancy times in each living state
    - $LE_{total} = LE_{no\ cognitive\ impaired\ (CI)} + LE_{slight\ CI} + LE_{severe\ CI}$
- LEs written as a function of the model parameters (integral)
- Piece-wise constant hazards (3 months) to account for the changing risk of transitions by age
- Confidence Intervals for LEs – simulate 50 MVN random vectors from the MLEs of model parameters

Jackson et al. (2003) *J R Stat Soc Ser D-Stat* 52(2):1-17

van den Hout et al. (2010) *J R Stat Soc Ser A Stat Soc* 173(2):331-349

LEs by education, occupation and social engagement

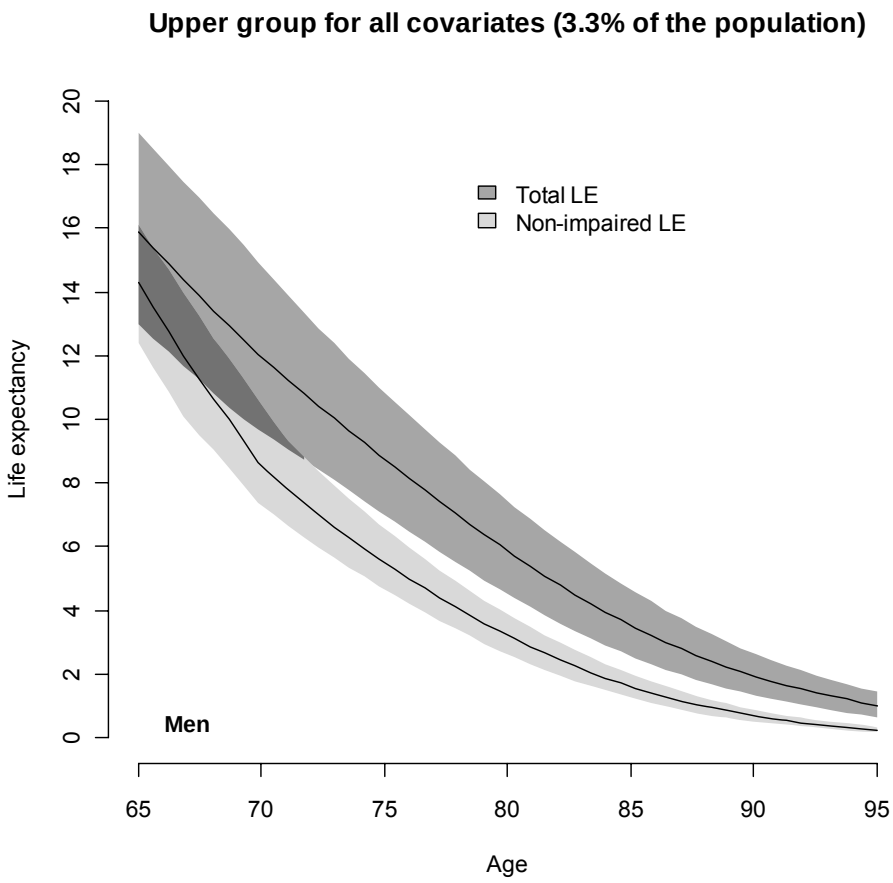


For a 65 year old man with low reserve*

- Mean LE = 12.8 yrs
- LE w/out cognitive impairment = 8.5 yrs
- Prop^{n} life w/out impairment = 66%

* in the youngest age cohort

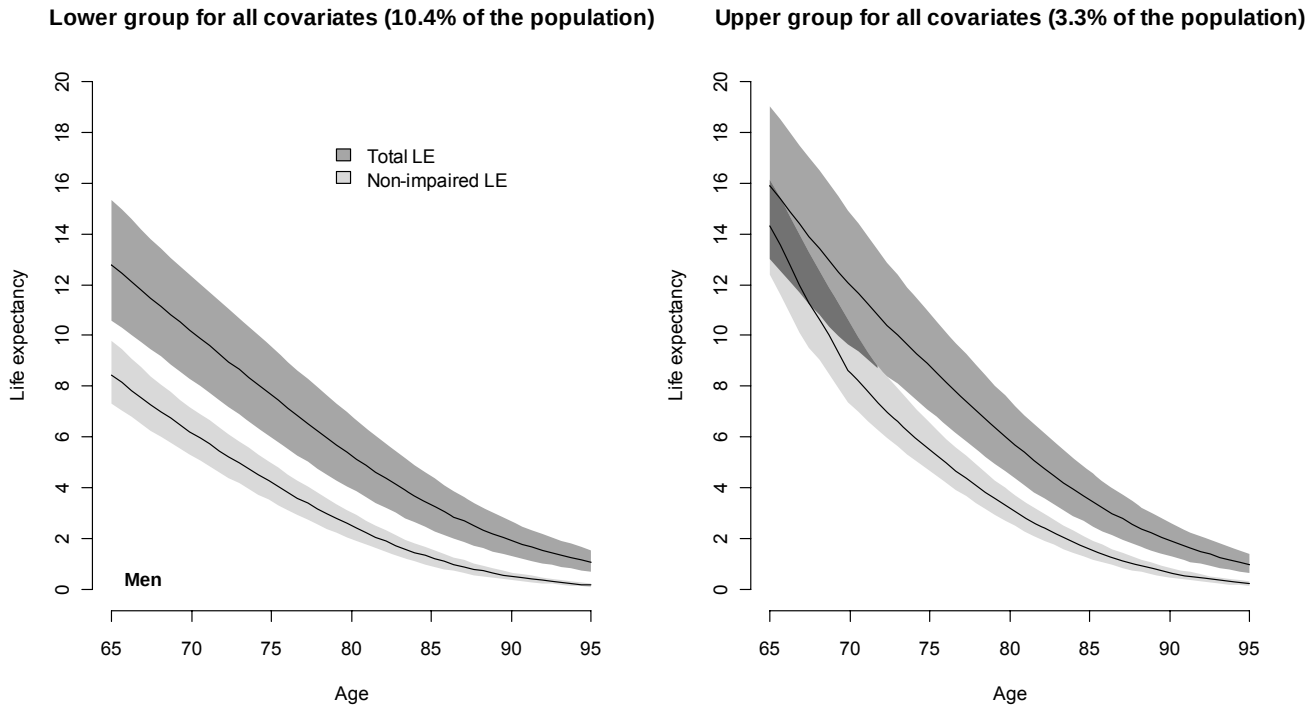
LEs by education, occupation and social engagement



For a 65 year old man with high reserve

- Mean LE = 15.9 yrs
- LE w/out cognitive impairment = 14.3 yrs
- Prop^{n} life w/out impairment = 90%

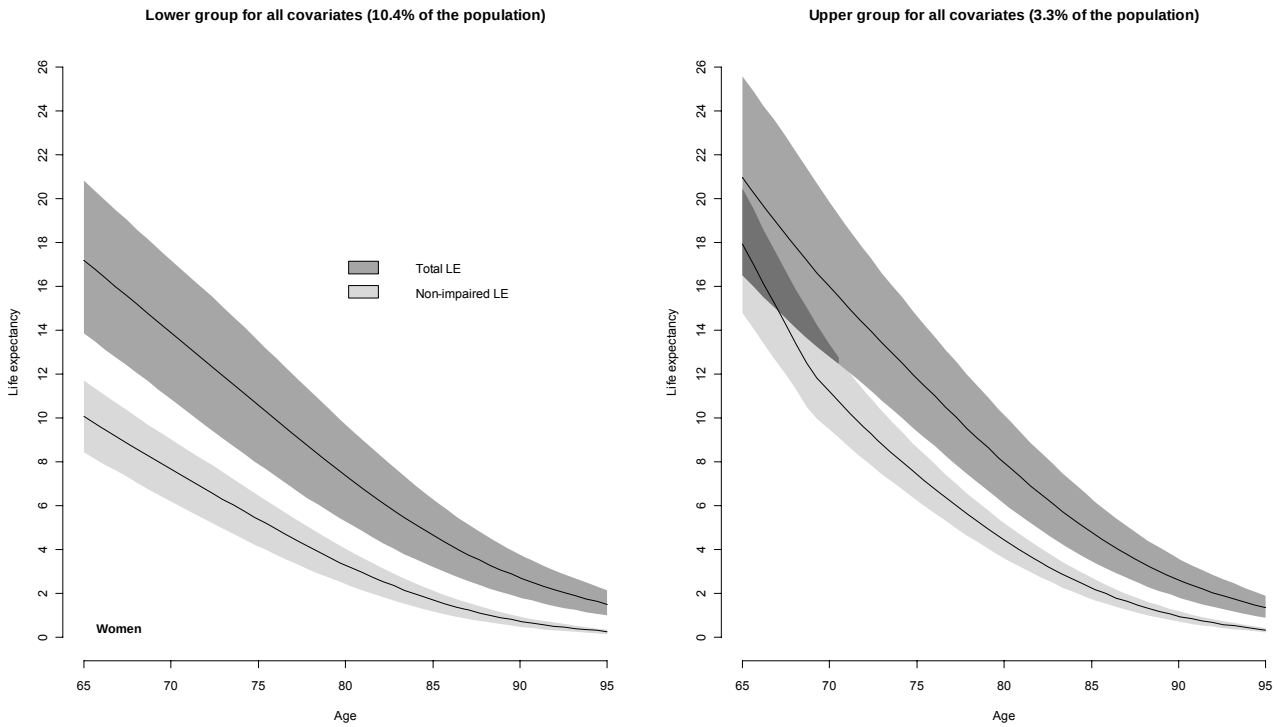
LEs by education, occupation and social engagement



For a 65 year old man with high versus low cognitive reserve

- Extra 3.1 yrs of total LE (24% increase)
- 5.8 yr increase in LE w/out cognitive impairment

LEs by education, occupation and social engagement



For a 65 year old woman with high versus low cognitive reserve

- Extra 21.0 – 17.2 = 3.8 yrs of total LE (22% increase)
- 7.9 yr increase in LE w/out cognitive impairment

Cognitive reserve and cognitive transitions

Model 4: Education + occupation + social eng.

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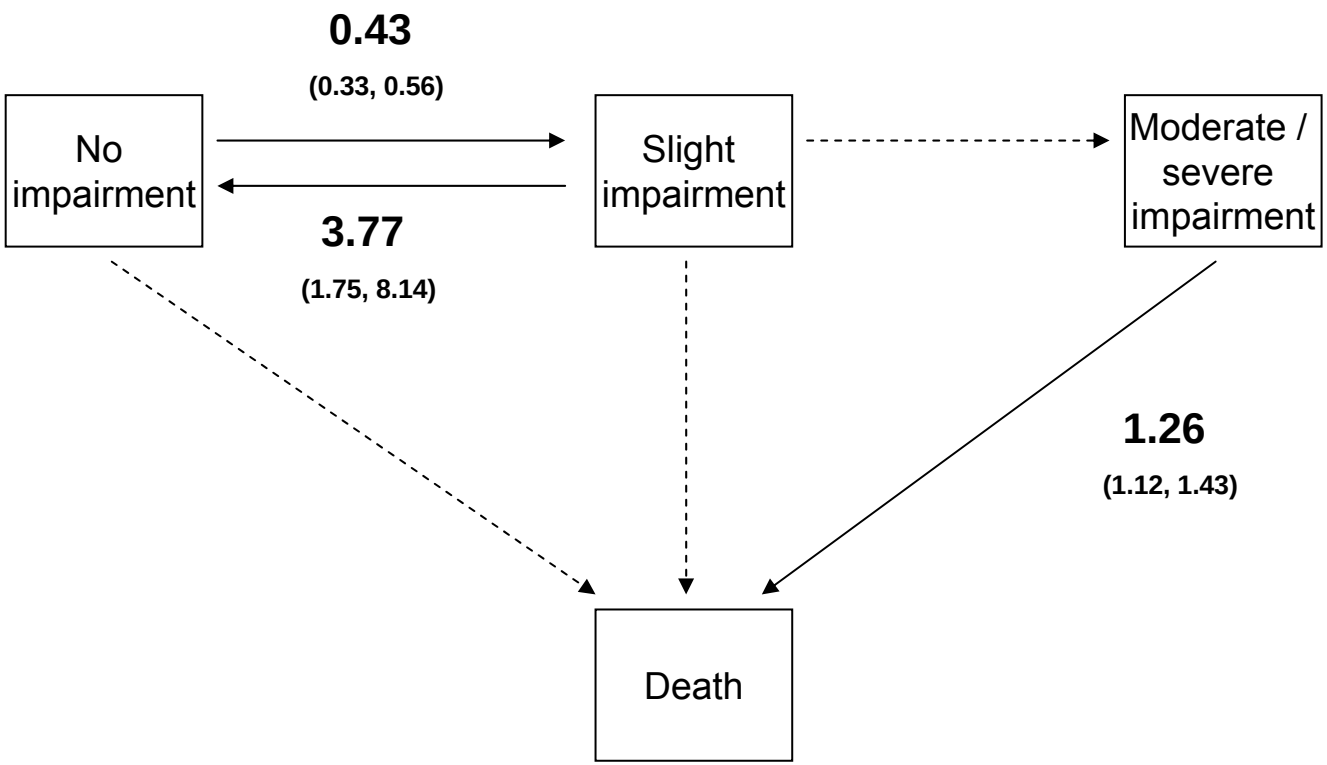
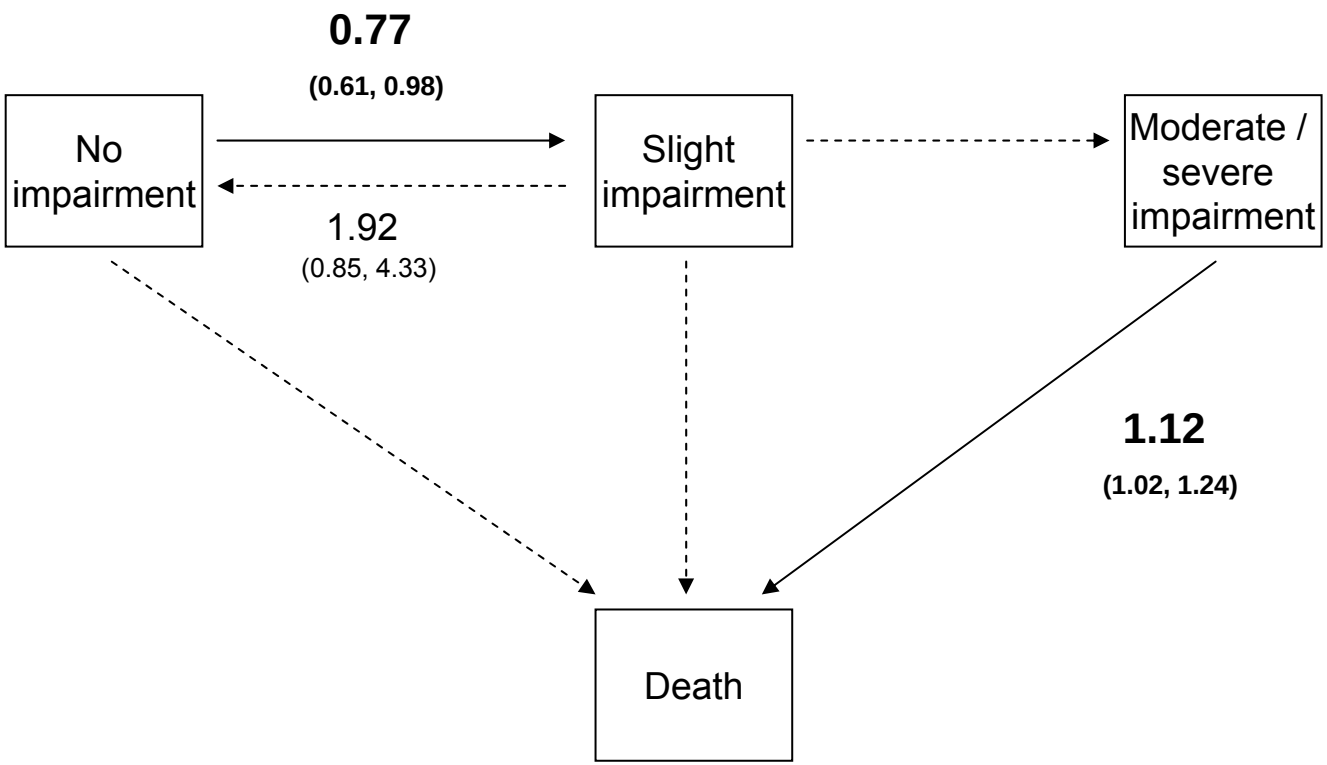
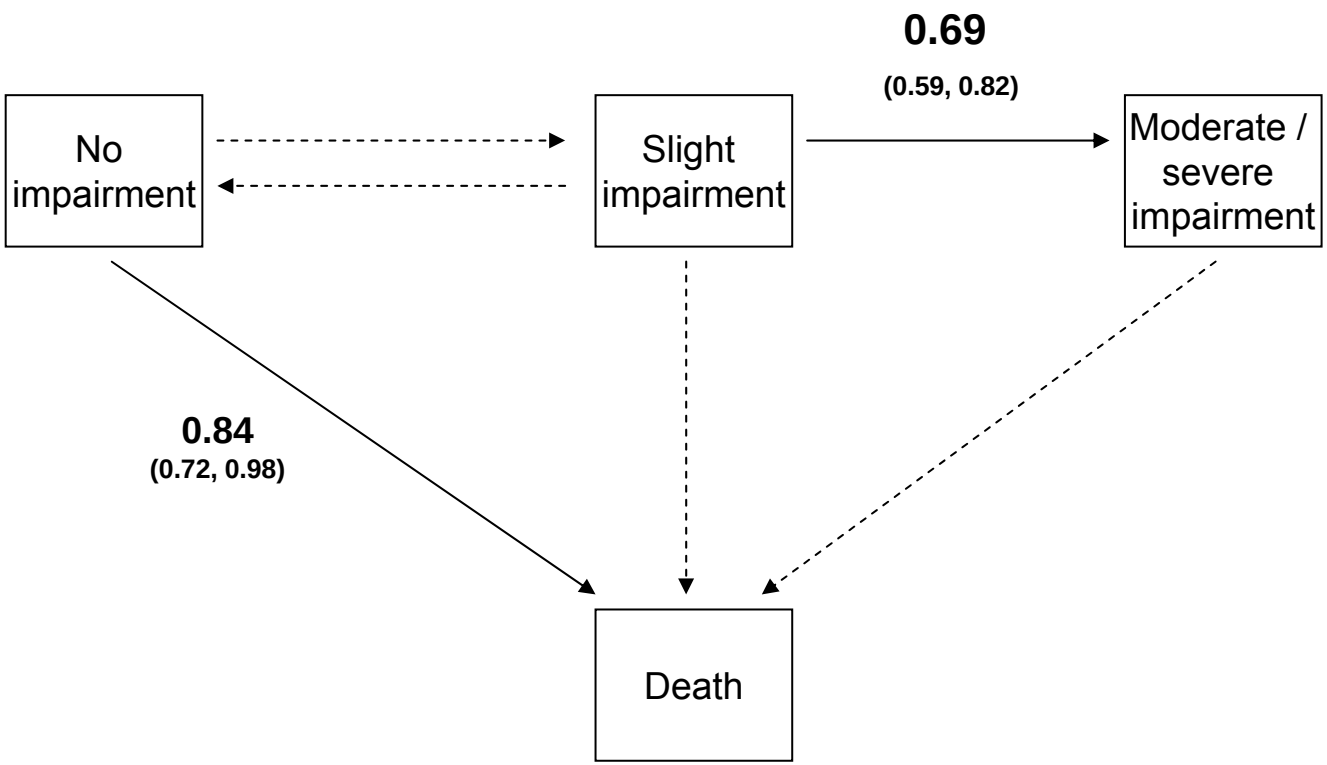


Model 4: Education + occupation + social eng.



Model 4: Education + occupation + social eng.



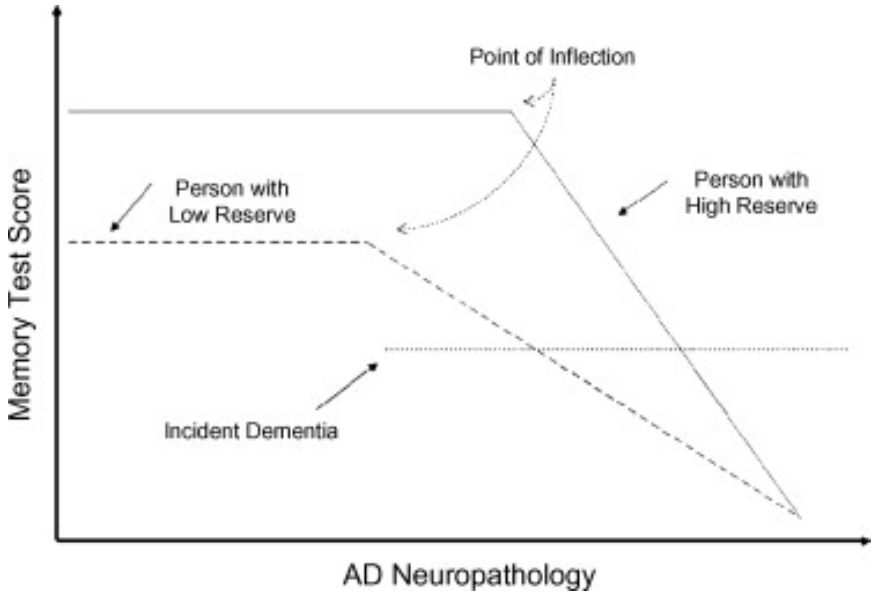
Summary of Results

- An enhanced cognitive reserve
  - **increases total and non-cognitively impaired life expectancy by ~25%**
  - slows cognitive decline
  - increases cognitive recovery from a slightly impaired state

  BUT…
  - accelerates the transition to death from a severely impaired cognitive state

- These associations are driven mainly by education
- Decreased social engagement ⟶ transition to severe cognitive impairment

Possible explanation - compensation



Stern (2009) *Neuropsychologia* 47(10);2015-28

Acknowledgements

University of Cambridge

Carol Brayne

Hannah Keage

Blossom Stephan

MRC Biostatistics Unit

Fiona Matthews

Ardo van den Hout

Chris Jackson

University of New South Wales

Michael Valenzuela

Funding

Medical Research Council

Alzheimer's Research UK

MRC CFAS participants and their families

MRC CFAS research team

www.cfas.ac.uk

Multi-state model (misclassification)

- Individual $i's$ contribution to the likelihood is

$$\Pr(X^*_{t_1}, ..., X^*_{t_m}) = \sum \Pr(X^*_{t_1}, ..., X^*_{t_m} \mid X_{t_1}, ..., X_{t_m}) \Pr(X_{t_1}, ..., X_{t_m})$$

(sum over all possible paths of latent states $X_{t_1}, ..., X_{t_m}$)

Multi-state model (misclassification)

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where

$$\Pr(X^*_{t_1}, ..., X^*_{t_m} \mid X_{t_1}, ..., X_{t_m}) = \Pr(X^*_{t_m} \mid X_{t_m}) \times ... \times \Pr(X^*_{t_1} \mid X_{t_1})$$

Multi-state model (misclassification)

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$$\Pr(X^*_{t_1}, ..., X^*_{t_m} \mid X_{t_1}, ..., X_{t_m}) = \Pr(X^*_{t_m} \mid X_{t_m}) \times ... \times \Pr(X^*_{t_1} \mid X_{t_1})$$

and

$$\Pr(X_{t_1}, ..., X_{t_m}) = \Pr(X_{t_m} \mid X_{t_{m-1}}) \times ... \times \Pr(X_{t_2} \mid X_{t_1}) \Pr(X_{t_1})$$