MRC Unit for Lifelong Health and Ageing

UCL

Lifetime severe affective symptoms and subsequent **cognitive state**: over 50 years of follow-up in the 1946 British Birth Cohort Study.

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Cognitive function

Ability:

- Remember, Learn, Concentrate, Plan, Think, Reason

Ageing -> Cognitive decline:

- Natural, gradual, ongoing and varying change in cognition as people age

Dementia:

- Set of symptoms including substantial memory loss and difficulties with thinking, problem-solving. Brain diseases -> e.g. Alzheimer's Disease

- Understanding who is at greatest risk is an important public health issue

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Background

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- Increased risk for later-life dementia in those with history of **depression** (*OR=1.90,1.55-2.33) and **anxiety** (+RR:1.57,1.02-2.42)
- Variation – frequency, incident timing, age onset

Relationship is unclear – e.g do affective problems:

- Directly cause cognitive impairment and decline? (E.g through neurotoxicity)
- Develop in response to emerging cognitive decline?
- Indicate risk of dementia and share an underlying aetiology?

Detailed life course understanding:

- Temporal, time periods, accumulation
- Prospective
- Longer follow-up periods

*Ownby et al. 2006 Arch Gen Psychiatry, +Gulpers et al. 2016 Am J Geriatr Psychiatry.

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Background

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Life course features

Affective problems:

- Severity
- Frequency? – accumulation?
- Incident timing of problems?

Cognition:

- Dementia
- Cognitive state pre dementia onset?
- Independent of prior cognitive ability?

Aim:

Investigate how affective problems across the life course relate to later-life cognitive state, independent of prior cognitive ability

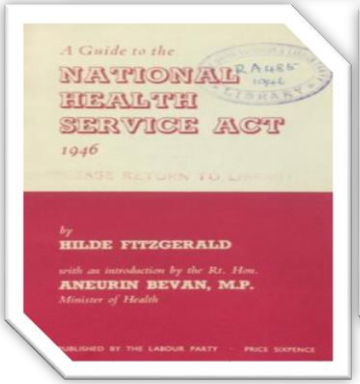
- Frequency/cumulative effect
- Incident timing

Methods - Cohort

MRC National Survey of Health and Development (British 1946 birth cohort)

History:

1946

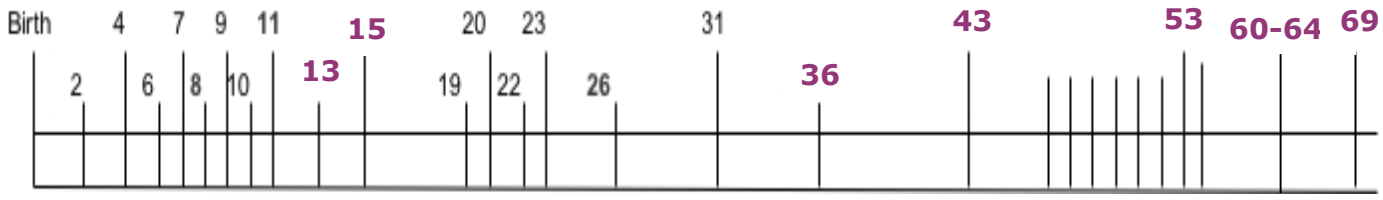


http://www.nshd.mrc.ac.uk/

Methods - Cohort

MRC National Survey of Health and Development (British 1946 birth cohort)

- Maternity study of all births in 1 week in March 1946
- Representative sample followed up (~5000)
- ~2800 in active follow-up



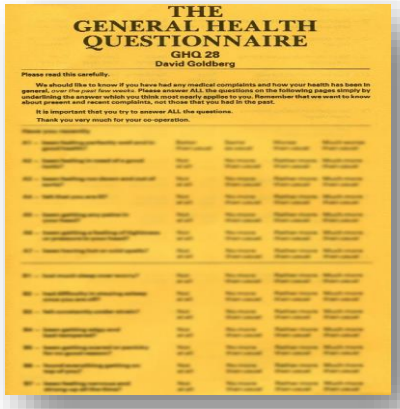
Methods - measures

Age

13-15

Affective ratings

Teacher ratings of emotional problems


THE GENERAL HEALTH QUESTIONNAIRE
GHQ 28
David Goldberg

Please read this carefully.

We should like to know if you have had any medical complaints and how your health has been in general, over the past few weeks. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

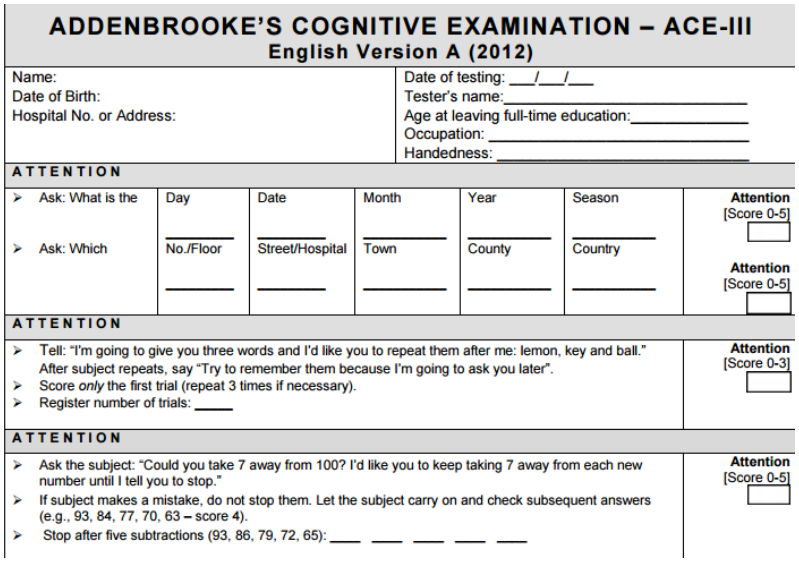
Thank you very much for your co-operation.

- Differing scales
- Validated thresholds

- **Cumulative effect across the life course**
  1. Meet threshold case-level
  2. Sum across testing waves
  3. Recode as follows:
     - Never case-level (reference)
     - Only once case-level
     - 2+ case-level

- **Different periods across the life course**
  - Never (reference)
  - Earlier-life only (pre 60)
  - Later-life only (post 60)
  - Earlier and later life

Methods - measures



ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III
English Version A (2012)

Name:
Date of Birth:
Hospital No. or Address:

Date of testing: ___/___/___
Tester's name:_____
Age at leaving full-time education:_____
Occupation: _____
Handedness: _____

ATTENTION

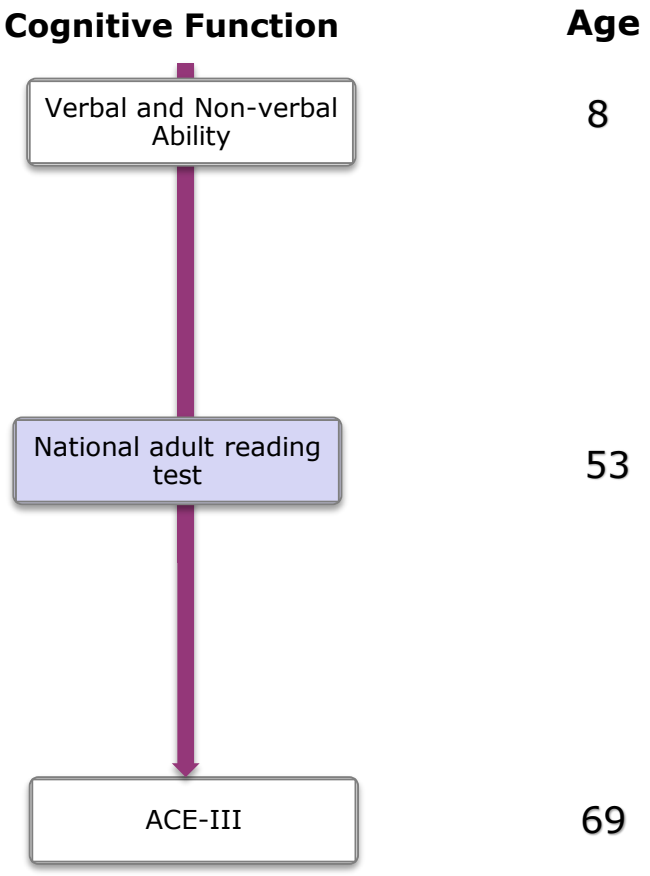
➢ Ask: What is the	Day	Date	Month	Year	Season	**Attention** [Score 0-5]
➢ Ask: Which	No./Floor	Street/Hospital	Town	County	Country	**Attention** [Score 0-5]

ATTENTION

➢ Tell: "I'm going to give you three words and I'd like you to repeat them after me: lemon, key and ball." After subject repeats, say "Try to remember them because I'm going to ask you later". **Attention** [Score 0-3]
➢ Score *only* the first trial (repeat 3 times if necessary).
➢ Register number of trials: ____

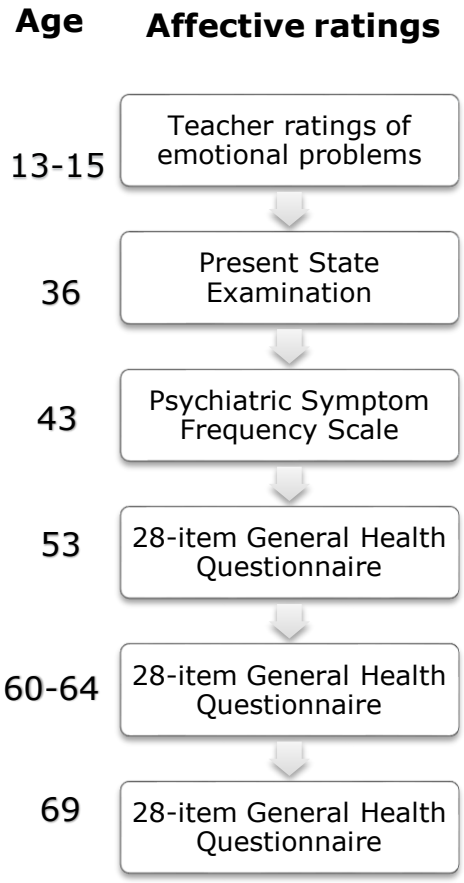
ATTENTION

➢ Ask the subject: "Could you take 7 away from 100? I'd like you to keep taking 7 away from each new number until I tell you to stop." **Attention** [Score 0-5]
➢ If subject makes a mistake, do not stop them. Let the subject carry on and check subsequent answers (e.g., 93, 84, 77, 70, 63 – score 4).
➢ Stop after five subtractions (93, 86, 79, 72, 65): ___ ___ ___ ___ ___



James SN et al. under review.

Methods - measures



Cognitive Function

ACE-III (age 69)

Aim:

Investigate how affective problems across the life course relate to later-life cognitive state

- Cumulative effect
- Incident timing

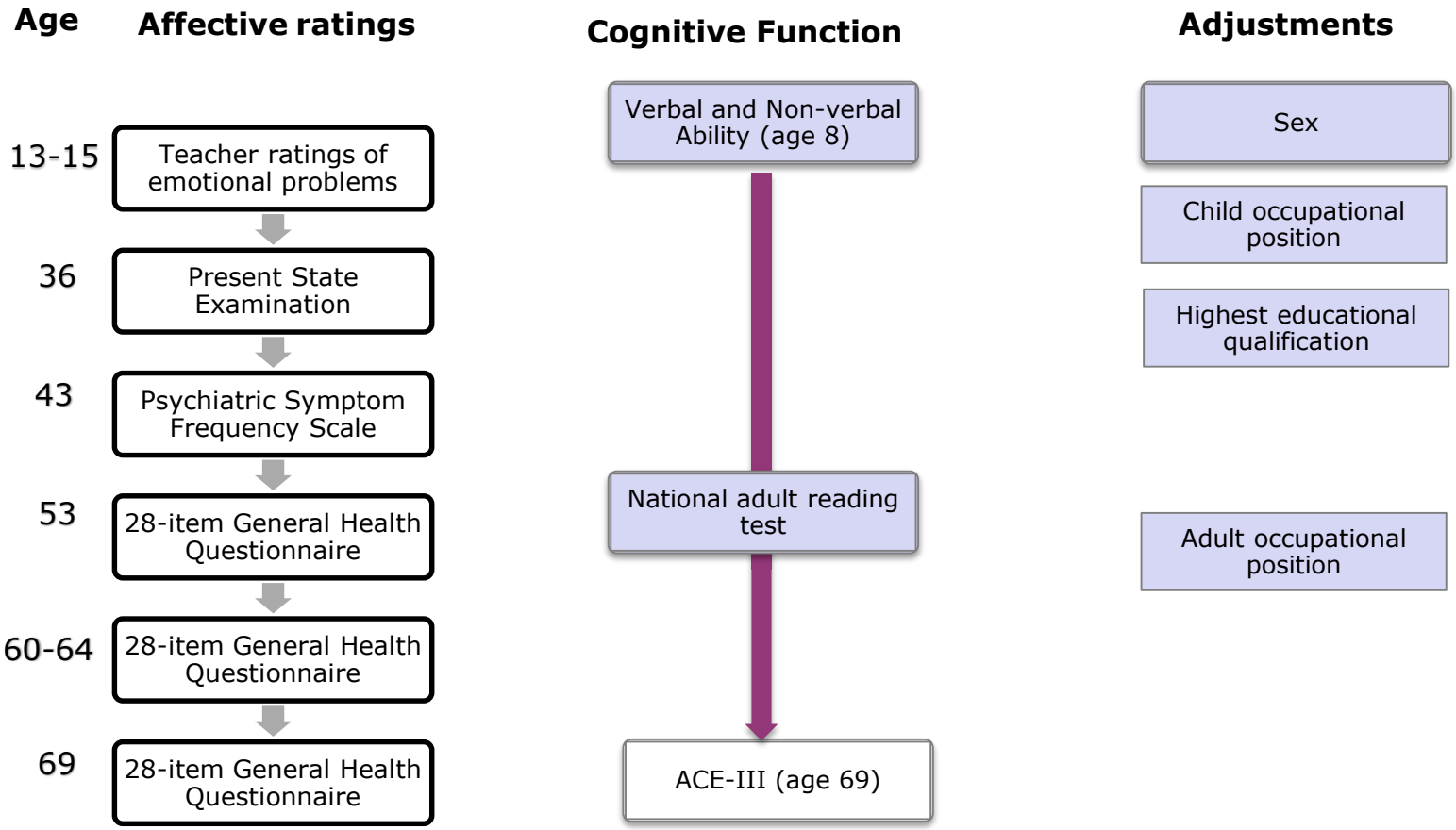
Analysis:

Multivariable linear regression analyses:

- Predictor categorical – with never case-level as a reference
- Outcome continuous – cognitive measures

James SN et al. under review.

Methods - measures



James SN et al. under review.

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Results – cumulative effect

UCL

Adjusted for sex, childhood cognition, child and adult occupational status, education, NART.

	Unadjusted		**Adjusted**	
	β	***95% CI***	**β**	***95% CI***
ACE-III scores *(n=1269)*				
Never case-level	*Reference*		*Reference*	
Once case-level	0.04	(-0.68,0.77)	-0.47	(-1.14,0.20)
≥2 times case-level	**-1.08**	**(-1.90,-0.25**)	**-0.91**	**(-1.68,-0.13**)

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Results – incident timing

UCL

Adjusted for sex, childhood cognition, child and adult occupational status, education, NART.

	Unadjusted		Adjusted	
	β	***95% CI***	**β**	***95% CI***
ACE-III scores *(n=1269)*				
Never case-level	*Reference*			
Case-level in earlier-life only	-0.04	(-0.73,0.80)	-0.33	(-1.06,0.40)
Case-level in late-life and earlier-life	**-1.36**	(**-2.31,-0.42**)	**-1.11**	(**-2.00,-0.23**)
Case-level in late-life only	-0.21	(-1.26,0.85)	-0.71	(-1.65,0.22)

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Summary

UCL

Cumulative effect:

- One severe affective problem was not assd with lower later-life cognitive state
- Two+ problems were assd with lower later-life cognitive state and function, controlling for prior cognition

Timing incidence:

- Affective problems in early- and late-life had the strongest assn with lower later-life cognitive state and function

Interpretation:

Suggests recurrent affective problems across the whole life course increases risk of diminished later-life cognitive state, when most SM are still free of dementia

- Window in early late-life when this risk becomes manifest
- Decline is accelerated by age 69 (Davis et al. 2017)
- ACE-III may have captured additional cognitive impairment

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Summary and conclusions

UCL

Limitations:

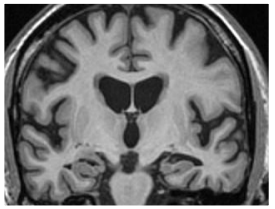
- Measures of affective symptoms differed; thresholds validated
- Reverse causation; controlled for prior cognition

Implications:

- Recurrent affective problems should be **monitored** for later-life diminished cognitive state
- **Effective management** of recurrent affective problems may reduce the risk of decreased cognitive function.

Future:

- Continued follow-up to determine if recurrent Sx raise dementia risk
- Mechanisms underlying association:
  - Increased Aβ plaques in affective disorders
  - Atrophy
  - Vascular disease
  - Inflammatory pathways



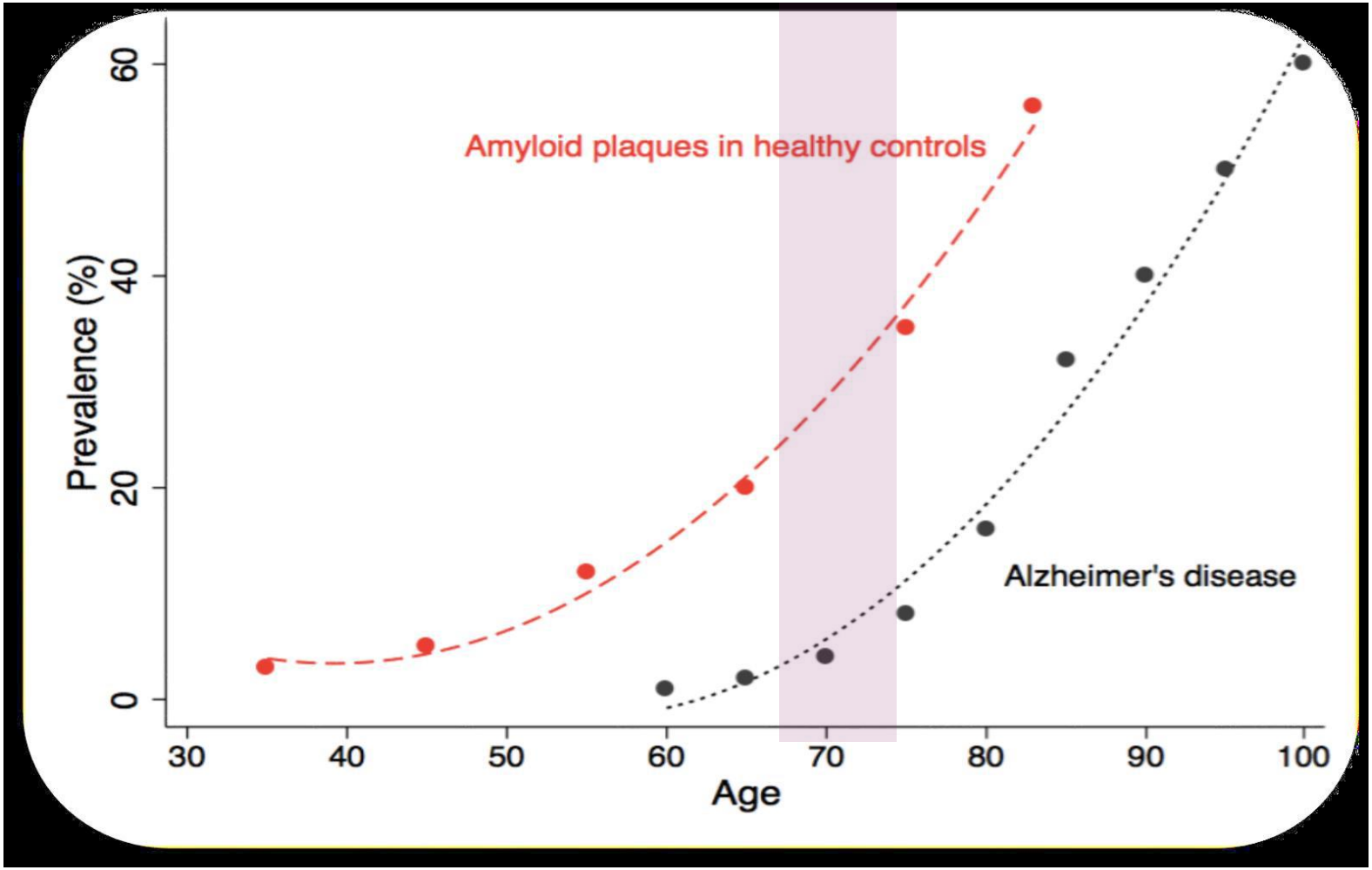
NSHD neuroscience sub-study: Insight46

- Random sample of 500 MRC NSHD individuals
- Attend UCL for detailed neurological and cognitive assessment x 2
- Amyloid PET (18F Florbetapir PET) and multi-modal MRI on a hybrid PET/MRI scanner

Siemens mMR Biograph hybrid PET/MR scanner

Age 69-71/71-73

- Few with clinical Sx
- More with pathology
- Preclinical window



NSHD neuroscience sub-study: Insight46

Assessments:

Clinical assessments

Neuropsychology

Sensory testing

Fluid biomarkers

Genetics

Brain donation requested

Neuroimaging

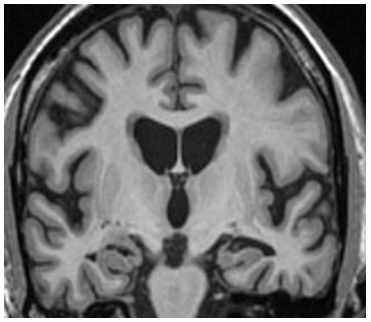
Imaging protocol:

Total acquisition time ~60 minutes

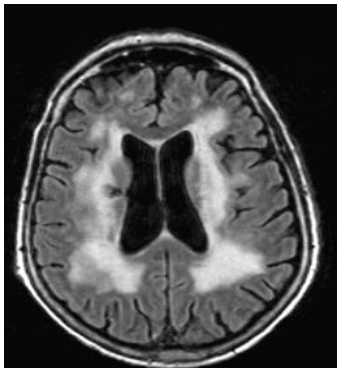
- Attenuation Correction sequences
- Volumetric T1
- Volumetric T2
- Volumetric FLAIR
- Resting state fMRI
- Field Mapping
- Multi-shell Diffusion Weighted Image
- Arterial Spin Labelling
- Susceptibility Weighted Image

Simultaneous acquisition of PET data using Florbetapir

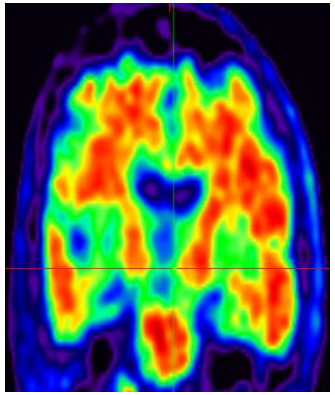
Pathology in vivo



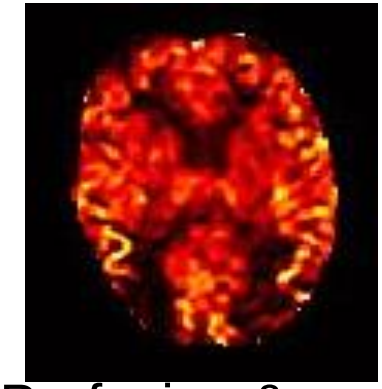
Structure



Vascular

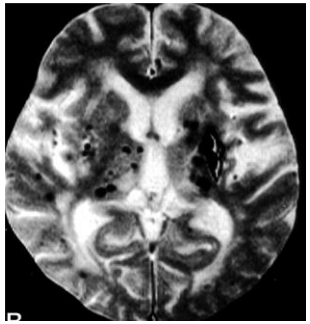


Amyloid load



Perfusion & activation

Networks



Microbleeds

BMC Neurology

STUDY PROTOCOL Open Access

Study protocol: Insight 46 – a neuroscience sub-study of the MRC National Survey of Health and Development

Christopher A. Lane[1†], Thomas D. Parker[1†], Dave M. Cash[1,2], Kirsty Macpherson[1], Elizabeth Donnachie[3], Heidi Murray-Smith[1], Anna Barnes[4], Suzie Barker[1], Daniel G. Beasley[2], Jose Bras[5,6], David Brown[4], Ninon Burgos[2], Michelle Byford[7], M. Jorge Cardoso[2], Ana Carvalho[4], Jessica Collins[1], Enrico De Vita[8,9], John C. Dickson[4], Norah Epie[1], Miklos Espak[2], Susie M. D. Henley[1], Chandrashekar Hoskote[8], Michael Hutel[1,2], Jana Klimova[1], Ian B. Malone[1], Pawel Markiewicz[2], Andrew Melbourne[2], Marc Modat[1,2], Anette Schrag[10], Sachit Shah[8,9], Nikhil Sharma[7,11], Carole H. Sudre[1,2], David L. Thomas[3,9], Andrew Wong[7], Hui Zhang[12], John Hardy[13], Henrik Zetterberg[5,14,15], Sebastien Ourselin[2], Sebastian J. Crutch[1], Diana Kuh[7], Marcus Richards[7], Nick C. Fox[1] and Jonathan M. Schott[1*]

Integrating life course and neuroimaging

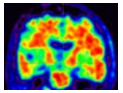
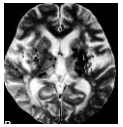
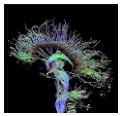
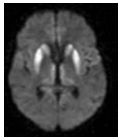
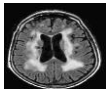
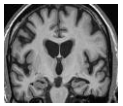
NSHD

Birth 1946 — Childhood — Adolescence — Early adulthood — Mid-adulthood — Later adulthood

DATA

- Cognitive function
- Cognitive function
- Temperament
- Mental health
- DNA
- epigenetic markers, telomere length, metabolites
- Infant feeding
- Diet
- Smoking, physical activity, alcohol and diet
- Social relationships & participation
- Survival; measured body size (height and weight); socioeconomic circumstances
- Health status
- Mother's experience of care
- Puberty, reproductive history & women's menopausal transition
- Blood pressure & lung function
- Developmental milestones
- Physical function

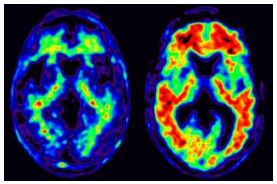
Insight46

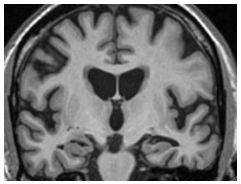







Neuroscience sub-study: Insight46 (N=500)

Age	Affective ratings
13-15	Teacher ratings of emotional problems
36	Present State Examination
43	Psychiatric Symptom Frequency Scale
53	28-item General Health Questionnaire
60-64	28-item General Health Questionnaire
69	28-item General Health Questionnaire
69-71	

Neuroimaging





Aβ load | Global Brain Volume

Research questions:

- Do those with affective Sx across specific periods, or across time, have differences in:
- Amyloid load?
- brain volume?
- Microbleeds?
- White matter hyper-intensities?

Identify those at risk and provide insight into underlying mechanisms of risk

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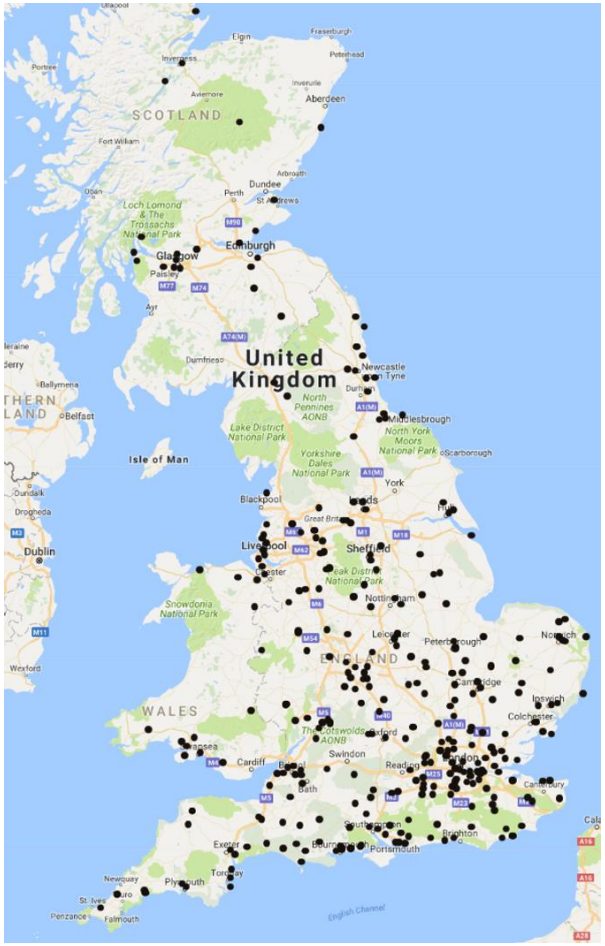
Insight46 Preliminary Results (n=240)

December 2016:

- 240 participants with analysable amyloid PET & MR data
- MMSE score 29.3 (±0.79, range=26-30)
- Males 50.9%
- Age: 70.1 years (range=69.3-70.8)
- 17.9% were Aβ+

- **January 2018:**
- 502 participants



MRC Unit for Lifelong Health and Ageing

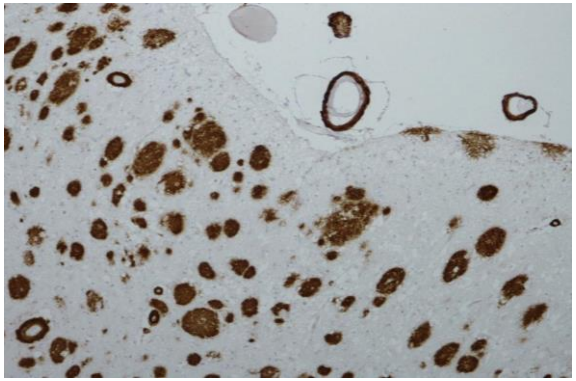
Thanks!

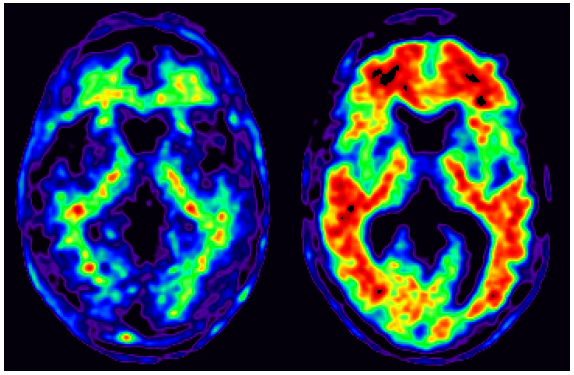
UCL

- Prof Marcus Richards
- Prof Diana Kuh
- Prof Rebecca Hardy
- Dr Daniel Davis
- Dr Celia O'Hare
- Dr Nikhil Sharma
- Dr Amber John
- Dr Darya Gaysina
- Dr Andy Wong and MRC LHA team
- NSHD participants
- Sponsors

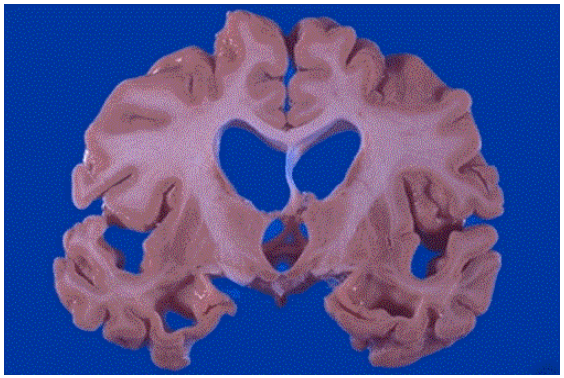
Neuropathology of AD

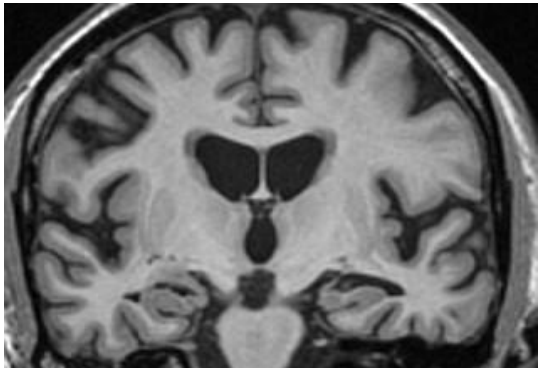
β-amyloid



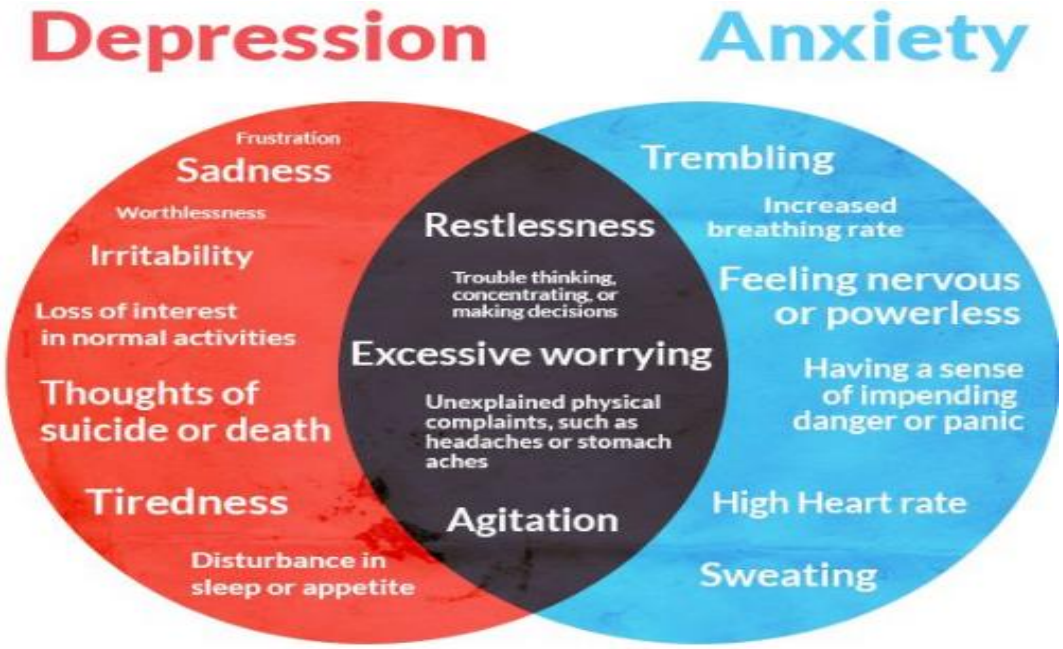


Atrophy





Affective problems



Affective problems

- Symptoms reach a certain threshold/criteria that impairs function
- 1/5 experience episode **during lifetime**
- Variation – frequency, incident timing, age onset

Zboniznek et al. 2013. Depress Anxiety

Table 1

DSM IV-TR Criteria for Adult MDD and GAD

MDD Criteria	GAD Criteria
A(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)	A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)
A(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)	B. The person finds it difficult to control the worry
A(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a moth), or decrease or increase in appetite nearly every day	***C(1) Restlessness or feeling keyed up or on edge****
A(4) Insomnia or hypersomnia nearly every day	***C(2) Being easily fatigued***
A(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)	***C(3) Difficulty concentrating or mind going blank***
A(6) Fatigue or loss of energy nearly every day	C(4) Irritability
A(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)	C(5) Muscle tension
A(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)	***C(6) Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)***
A(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	

*Bold and italicized symptoms are shared between GAD and MDD

Zboniznek et al. 2013. Depress Anxiety

Insight 46 – aims

To determine:

- The biomarker changes in very early AD
- The influence of other pathologies
- The life course and genetic influences on the onset and progression of cognitive decline

To provide:

- An evidence base for pre-dementia trial design
- A resource for ageing/dementia research

Fluid biomarker collection

- Bloods analysed for:
  - FBC, renal function,
  - B12, TSH
- Samples stored for later biomarker analysis

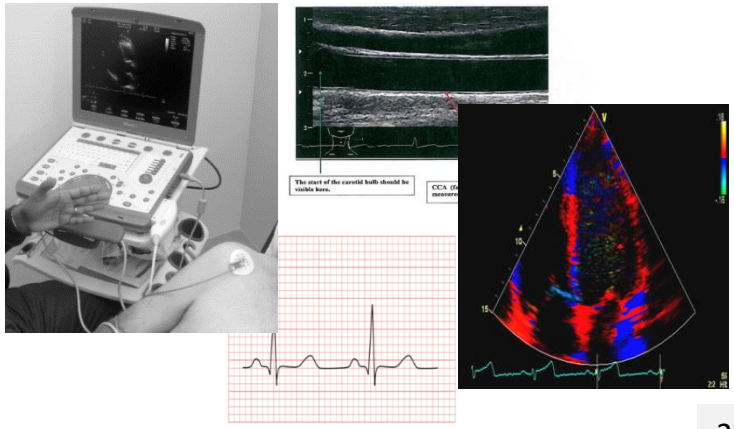
NSHD neuroscience sub-study: Minimal dataset

- Attendance at a clinic visit at age 60-64
- Parental occupational social class or education
- Memory and processing speed at 60-64 year collection AND at either ages 8, 11 or 15
- Height and weight at ages 4-15
- Highest qualification by age 26
- Mental health: adolescent teacher ratings
- Affective symptoms; BP; lung function; BMI; weight; smoking; exercise at 36, 43, 53 or 60-64
- Blood: either age 53 or 60-64 samples

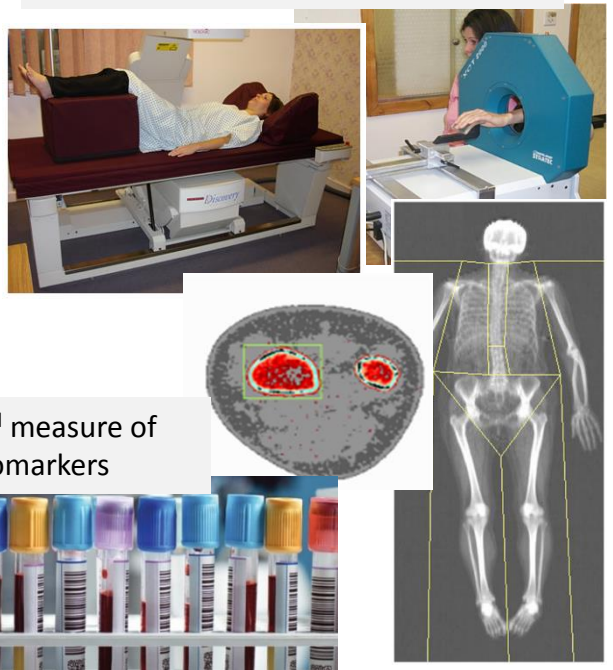
What has been measured? (ii)

Detailed clinical assessment at age 60-64 years: advancing the study of ageing

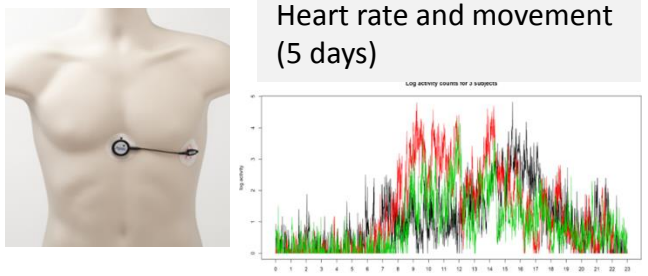
Cardiovascular structure and function



Body composition (incl. bone mineral density and fat and muscle mass)



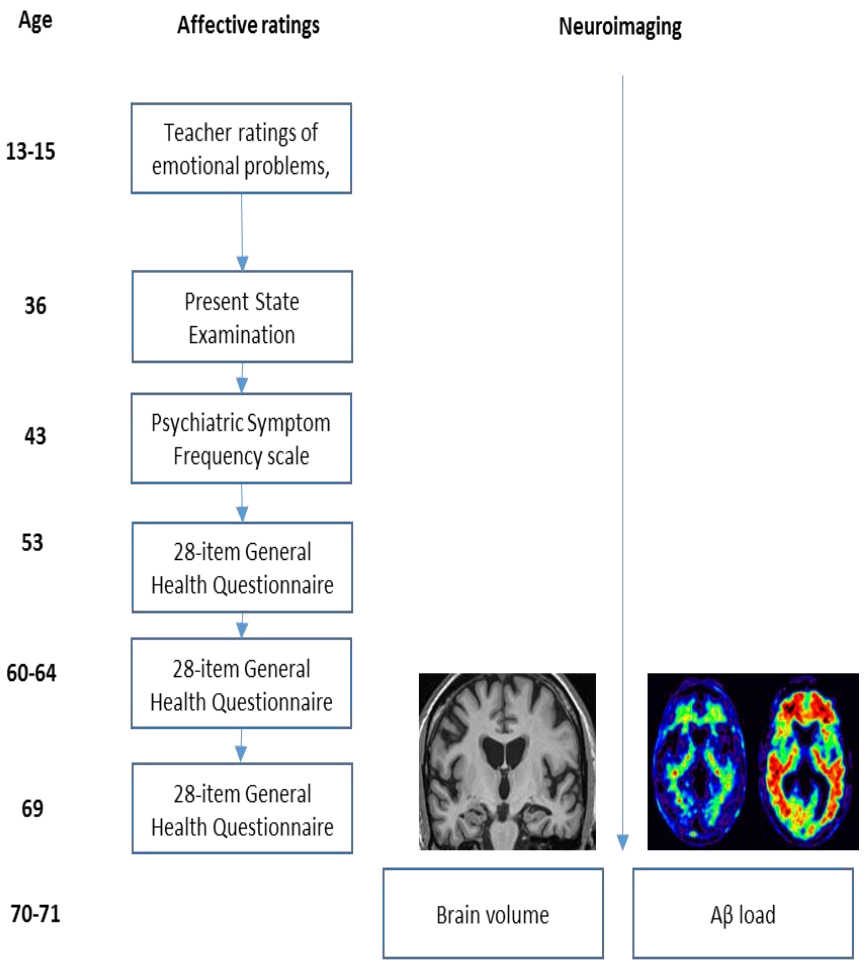
Heart rate and movement (5 days)



2nd measure of biomarkers

For more details see: Kuh et al, IJE 2011;40:e1-e9

Insight46 Preliminary analysis (n=240)



Affective symptoms:

- Standardised each measure
- Analysed as continuous variables
- Dichotomised at validated thresholds and sum

Neuroimaging outcomes

- Amyloid status – multivariable logistic regression
- Brain volume – multivariable linear regression

Adjustments

- Sex, socioeconomic position, smoking, (TIV)
- With and without APOE status

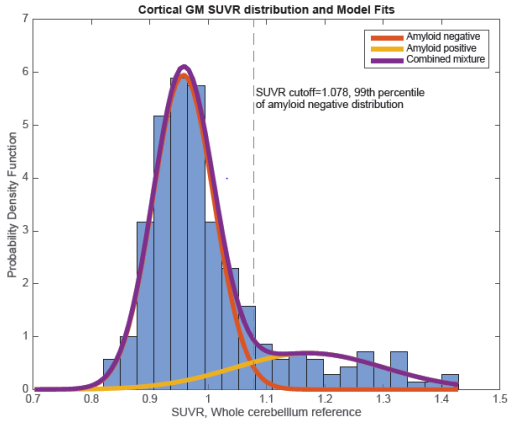
Insight46 – Neuroimaging quantification*

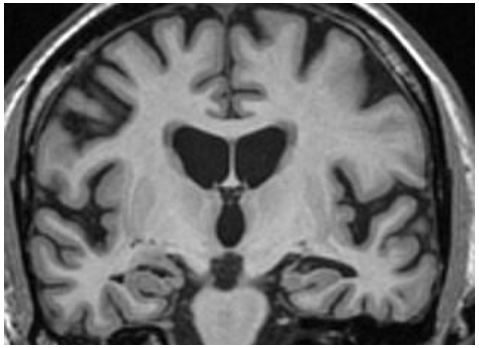
Amyloid:

- Binary measure Aβ+ status
- *Cortical grey matter SUVR with cerebellar reference
- Aβ+ SUVR threshold=>1.078
- 17.9% were Aβ+

Global brain volume:

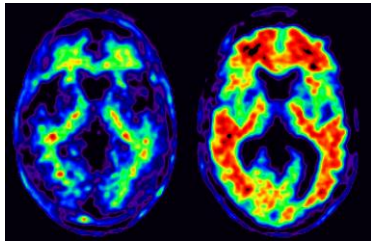
- *Calculated from parcellation of volumetric T1 scans





*See team talks/posters #Cash #Schott #Parker

Insight46 Preliminary Results (n=240): Lifecourse Affective Symptoms and Aβ+ at 70



No adjustments

Variable	OR	*95% CI*	*p*	*n*
Affective symptoms at 13-15	0.83	0.64,1.10	0.19	227
Affective symptoms at 36	1.14	0.84,1.55	0.40	227
Affective symptoms at 43	1.01	0.97,1.06	0.64	224
Affective symptoms at 53	1.03	0.95,1.11	0.52	236
Affective symptoms at 60-64	1.03	0.94,1.12	0.52	237
Affective symptoms at 69	1.07	0.96,1.19	0.22	238
Cumulative effect:				
Never case-level	Reference			
Once case-level	0.82	0.34,1.95	0.65	213
2+ case-level	1.35	0.49,3.73	0.56	213

- Having higher affective Sx in the life course is **not** associated with amyloid+

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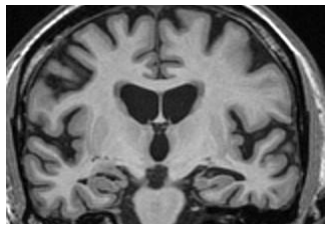
Insight46 Preliminary Results (n=240): Lifecourse Affective Symptoms and brain volume at 70



No adjustments apart from total intracranial volume

Variable	β	*95% CI*	*p*	*n*
Affective symptoms at 13-15	-0.01	-0.08,0.05	0.67	227
Affective symptoms at 36	0.02	-0.04,0.08	0.49	227
Affective symptoms at 43	-0.01	-0.07,0.05	0.76	224
Affective symptoms at 53	**-0.08**	**-0.02,-0.14**	**0.01**	236
Affective symptoms at 60-64	0.01	-0.05,0.07	0.81	237
Affective symptoms at 69	0.02	-0.04,0.08	0.48	238
Cumulative effect:				
Never case-level	Reference			
Once case-level	0.02	-0.17,0.14	0.85	213
2+ case-level	0.05	-0.15,0.26	0.61	213

- Having higher affective Sx with smaller brain volume
- Having more affective episodes in the life course was not associated with smaller brain volume

Insight46 **Preliminary Results**: Discussion

Preliminary!

Affective Sx:

Some association with smaller brain volume but not with **amyloid load**;

- Not related to amyloid and not AD?
- Related to brain volume? (and cog.function)
- Midlife important for smaller brain volume?

Future work:

- Explore in first full wave of Insight46 (n=500)
- Explore amyloid as a continuous, and non linear variable (#Parker)
- Explore relationship between affect, brain volume and cognition
- Investigate other mechanisms – e.g inflammatory, vascular
- Explore as AD-pathology changes in longitudinal follow-up of Insight46

Lifetime antecedents of cognitive state: seven decades of a birth cohort study

Professor Marcus Richards

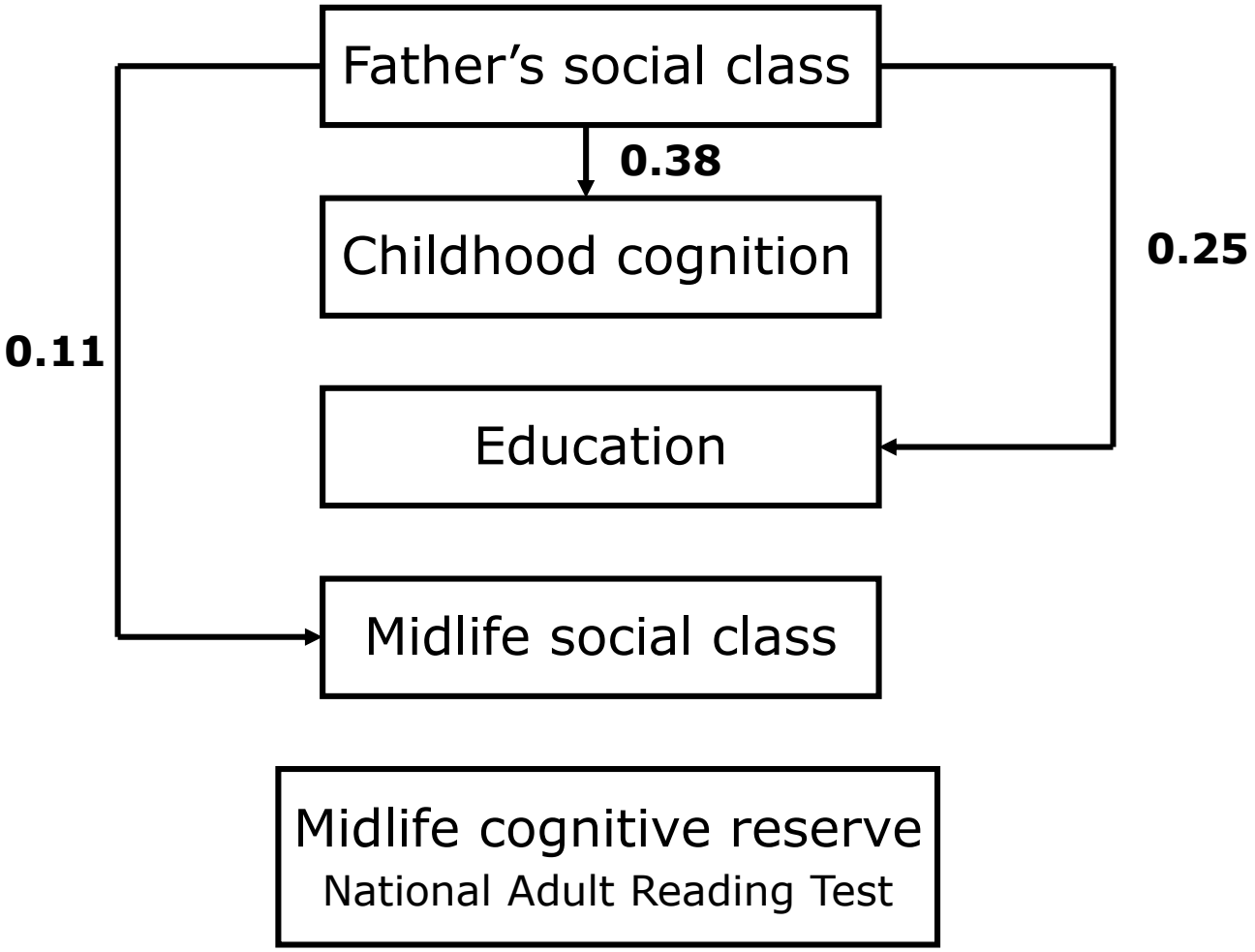
MRC Unit for Lifelong Health and Ageing at UCL

University College London

Towards a life course framework

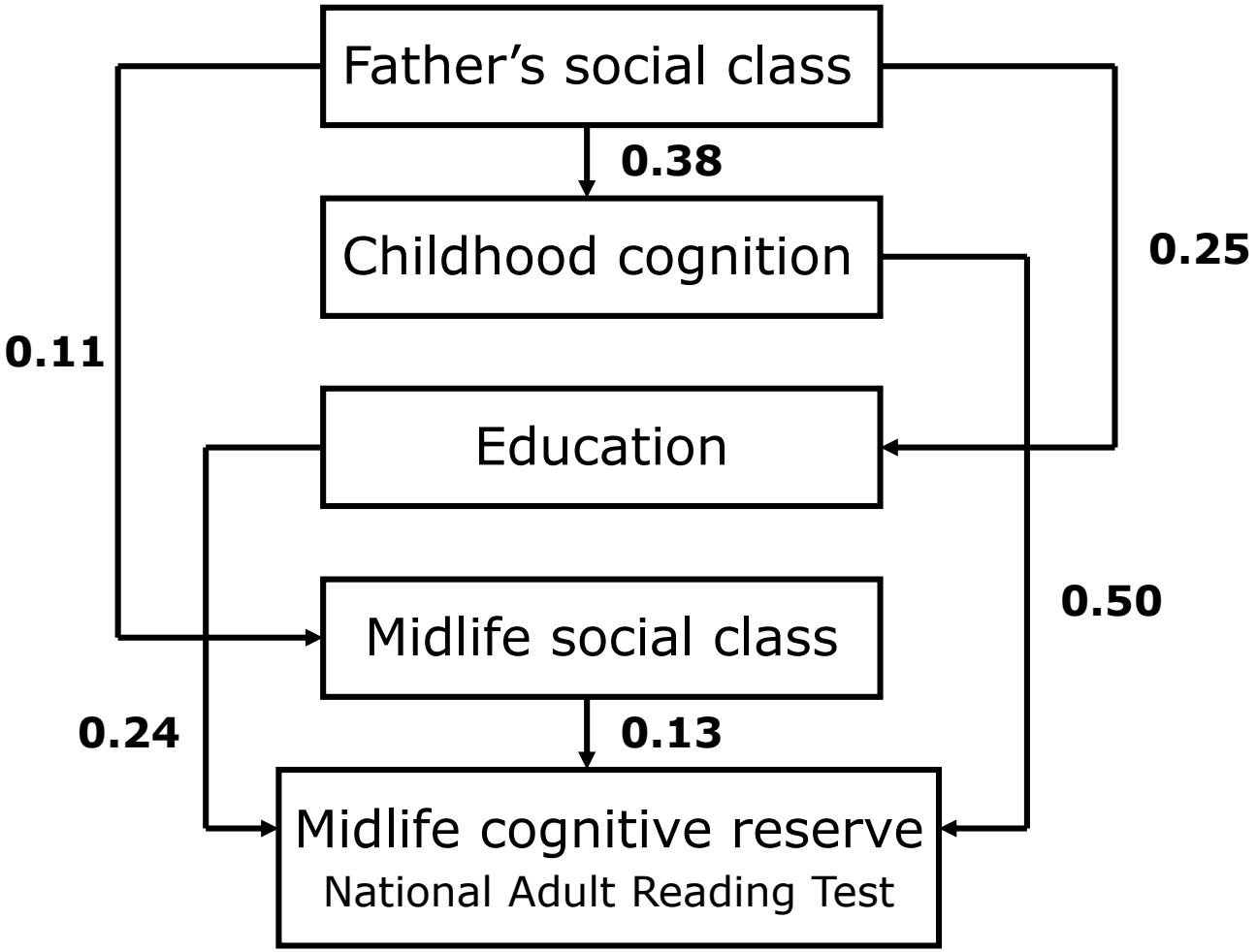
Some basic scaffolding

A basic life course path model for cognitive reserve



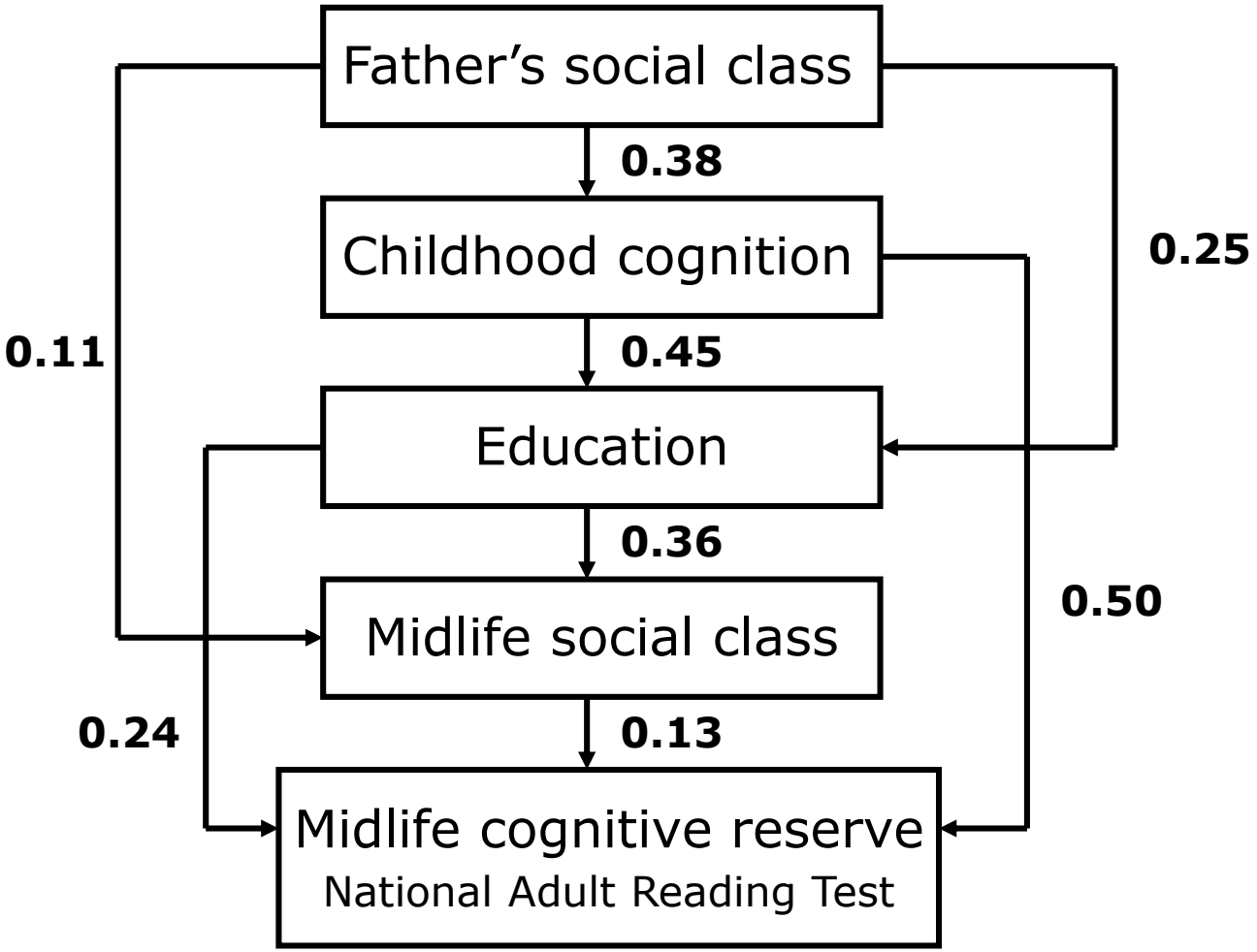
Richards & Sacker, J Clin Exp Neuropsychol 2003

A basic life course path model for cognitive reserve



Richards & Sacker, J Clin Exp Neuropsychol 2003

A basic life course path model for cognitive reserve



Richards & Sacker, J Clin Exp Neuropsychol 2003

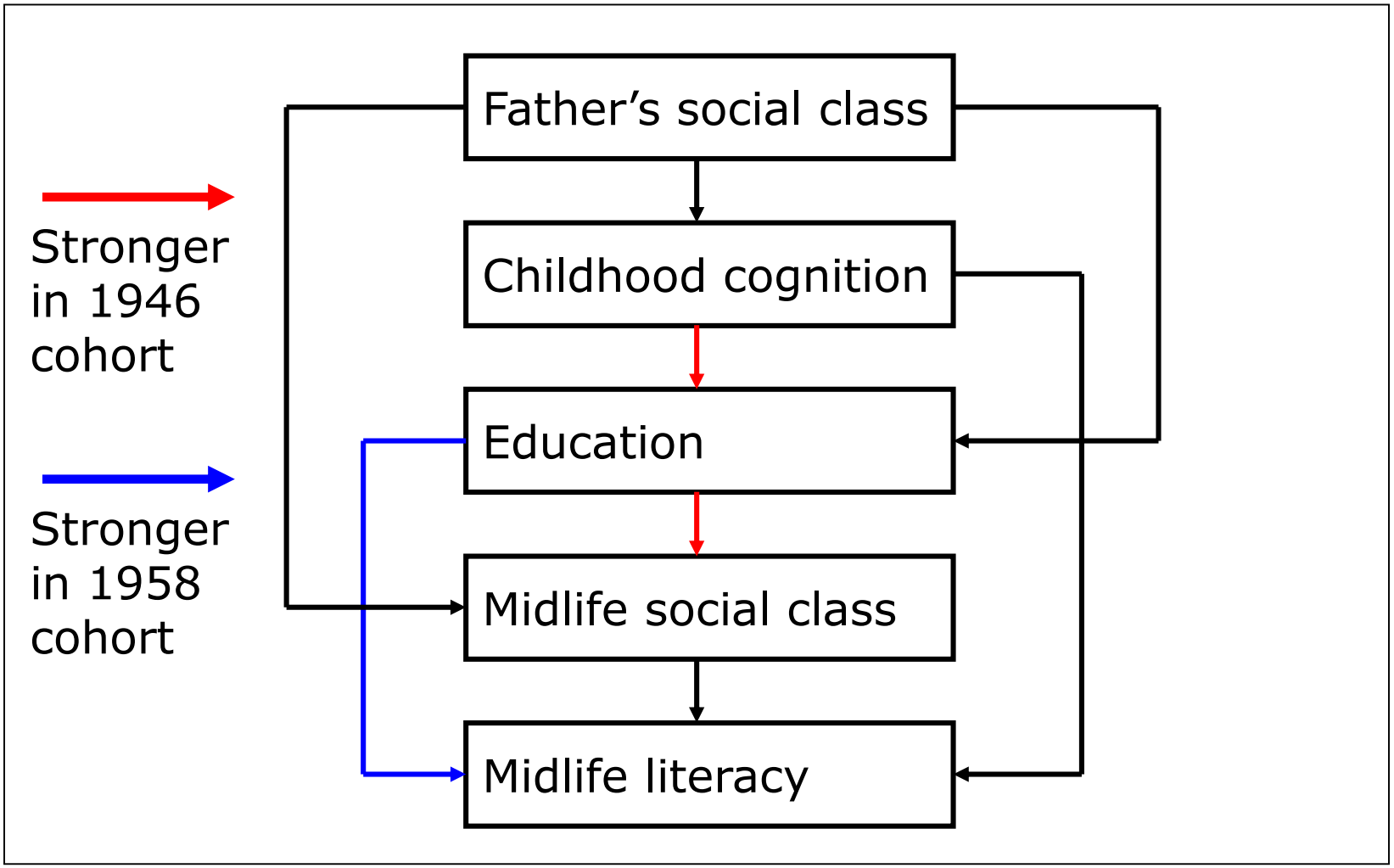
National Adult Reading Test (NART)

1. CHORD
2. ACHE
3. DEPOT
4. AISLE
5. BOUQUET

15. CATACOMB
16. GAOLED
17. THYME
18. HEIR
19. RADIX
20. ASSIGNATE

31. FACADE
32. ZEALOT
33. DRACHM
34. AEON
35. PLACEBO

45. PRELATE
46. SIDEREAL
47. DEMESNE
48. SYNCOPE
49. LABILE
50. CAMPANILE



Richards, Power & Sacker, J Epidemiol Community Health 2009

Addenbrooke's Cognitive Examination (ACE-III)

The most comprehensive test of mental state available

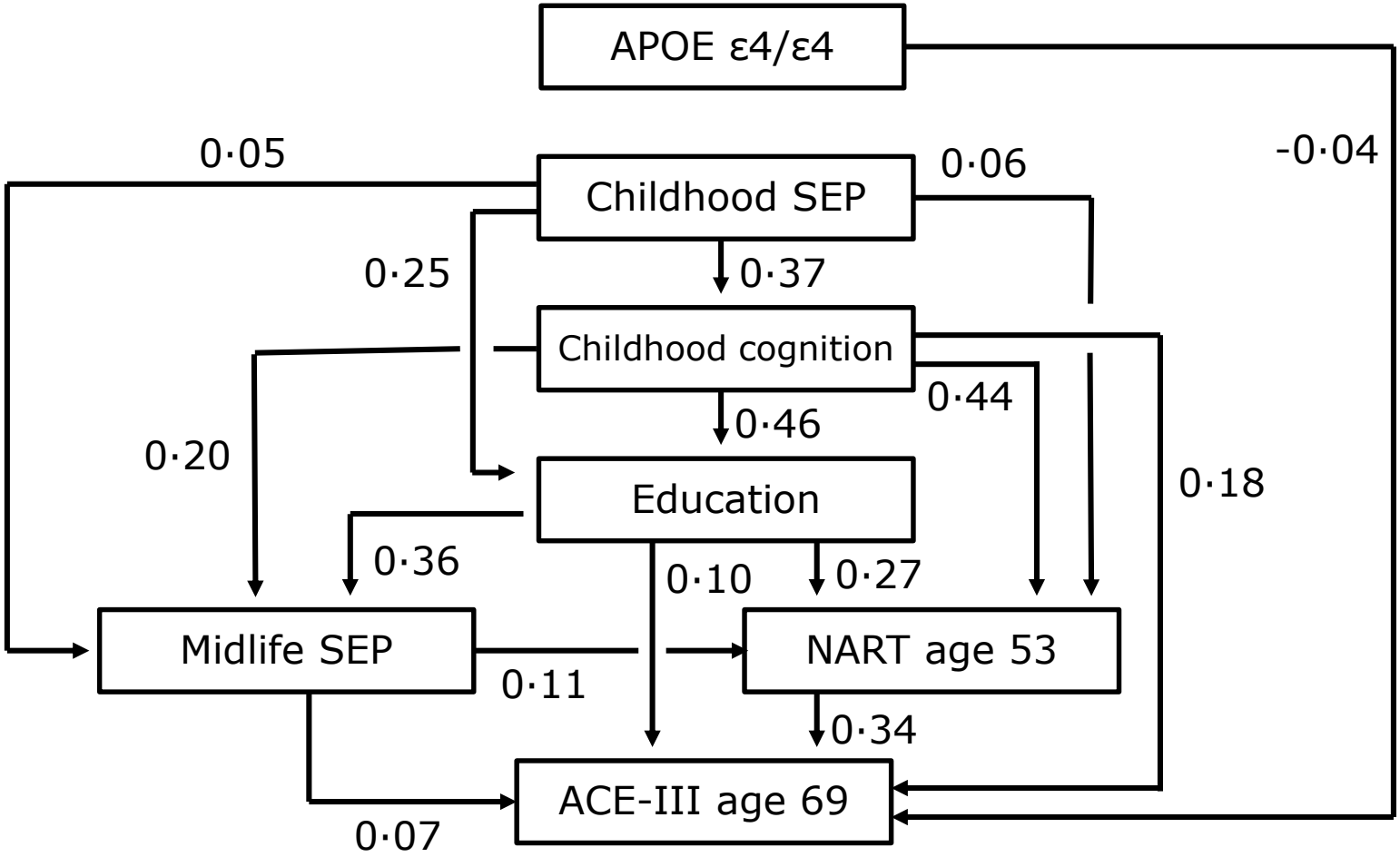
Screen-implemented

Five domains tested:

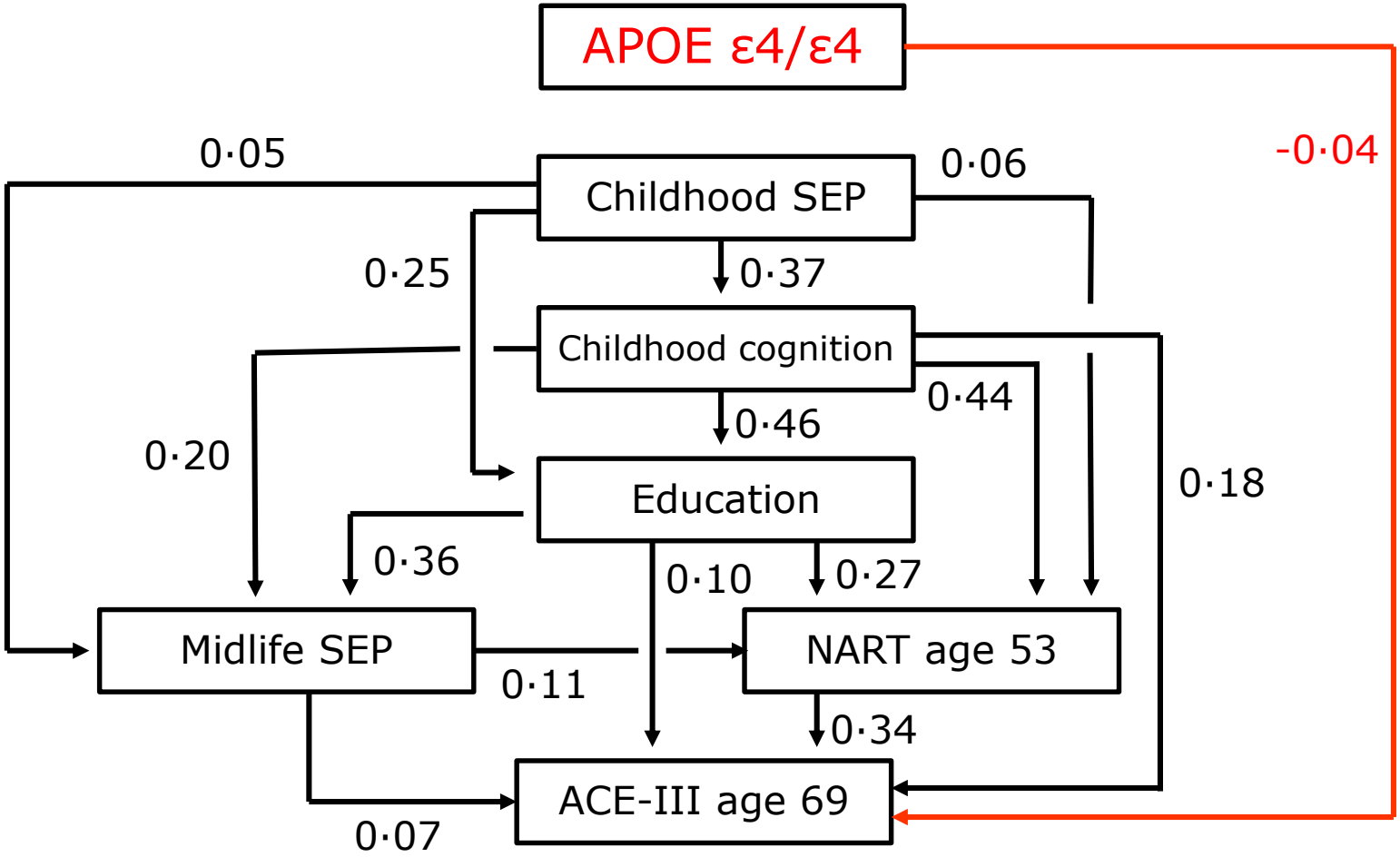
- Attention & orientation (0-18)
- Verbal fluency (0-14)
- Memory (0-26)
- Language (0-26)
- Visuospatial function (0-16)

Maximum total score = 100, with quasi-normal distribution

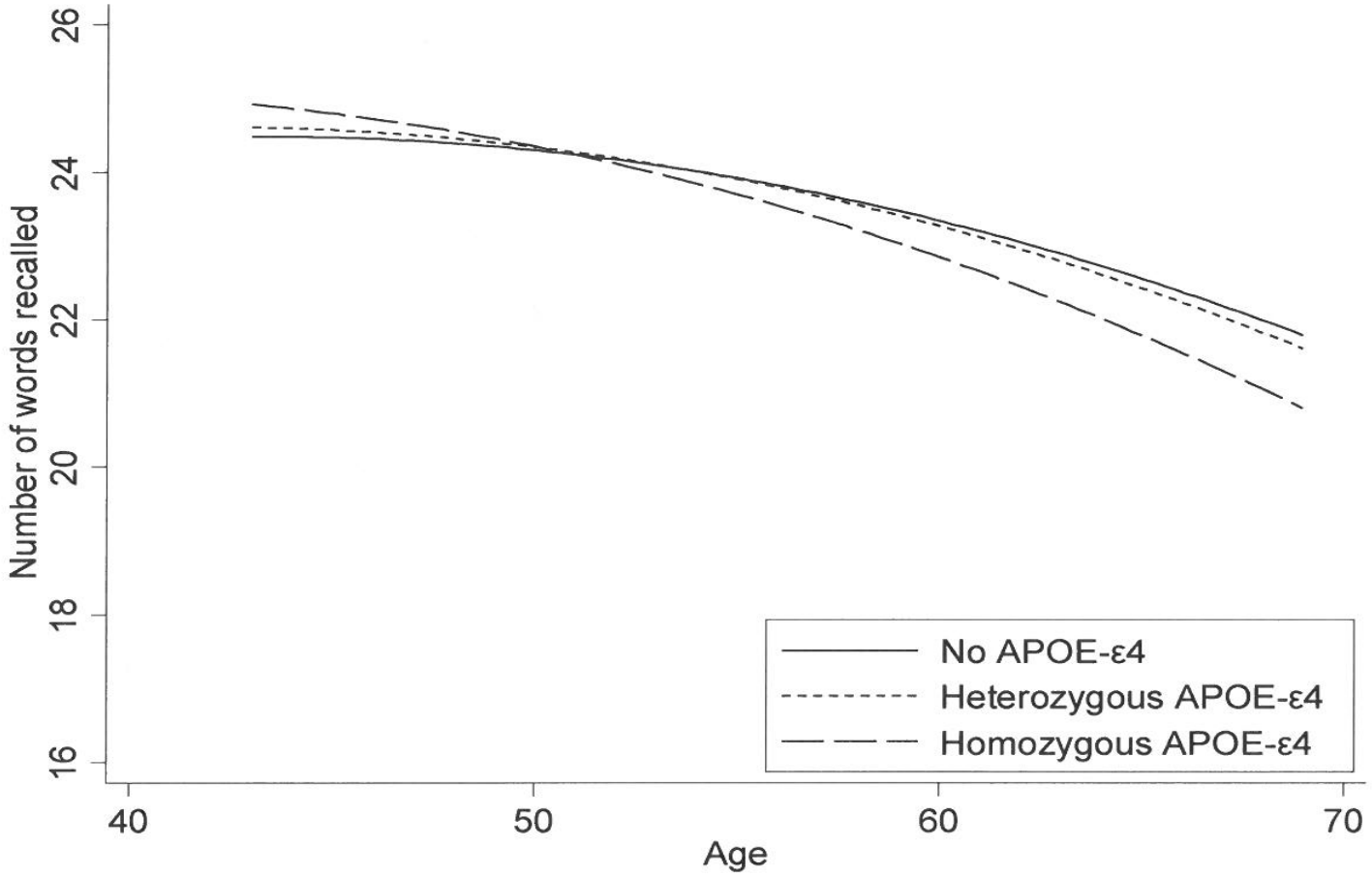
An updated path model for mental state at age 69



An updated path model for mental state at age 69

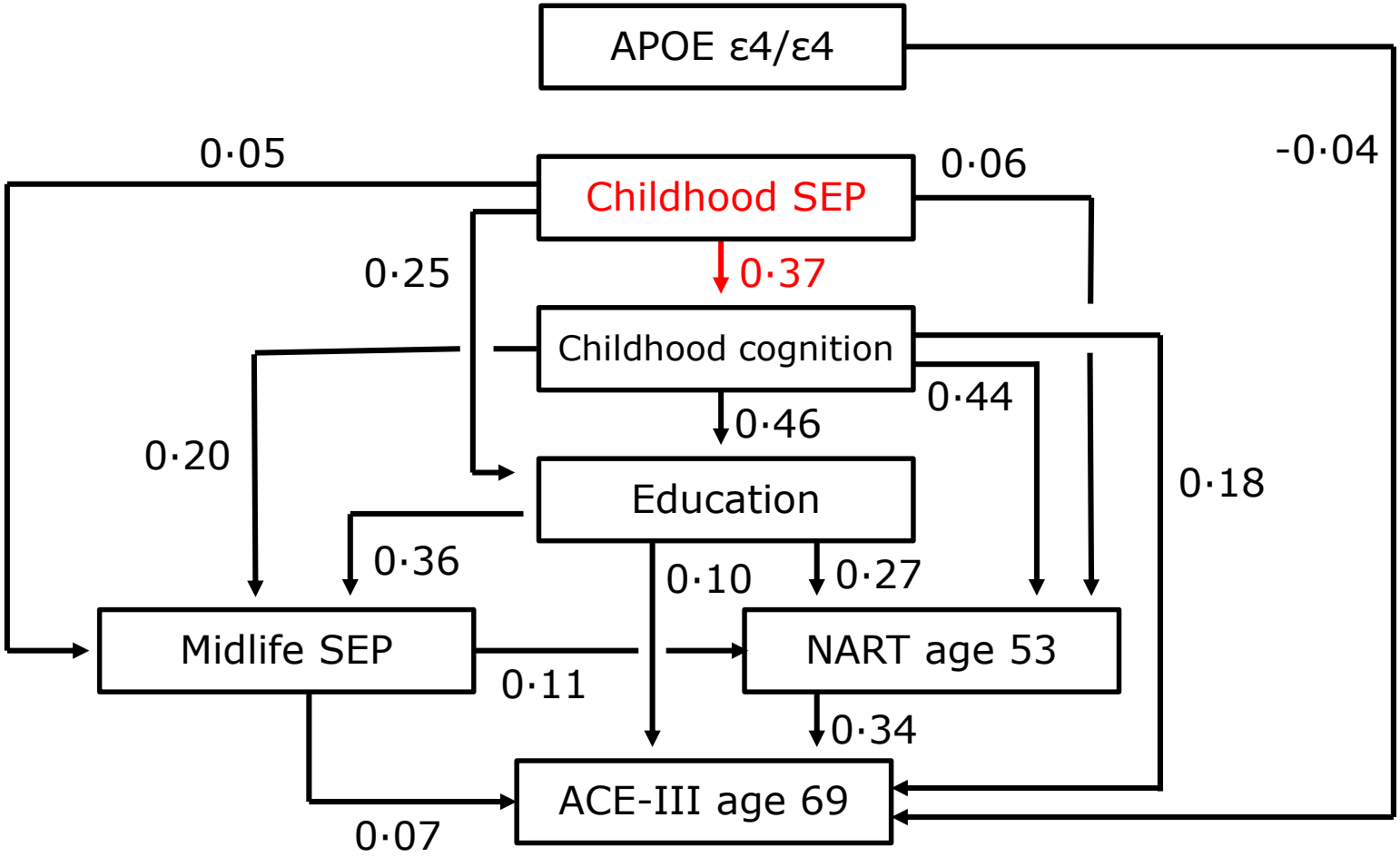


NSHD: Trajectory of verbal memory (word learning score) between ages 43 and 69 by APOE status

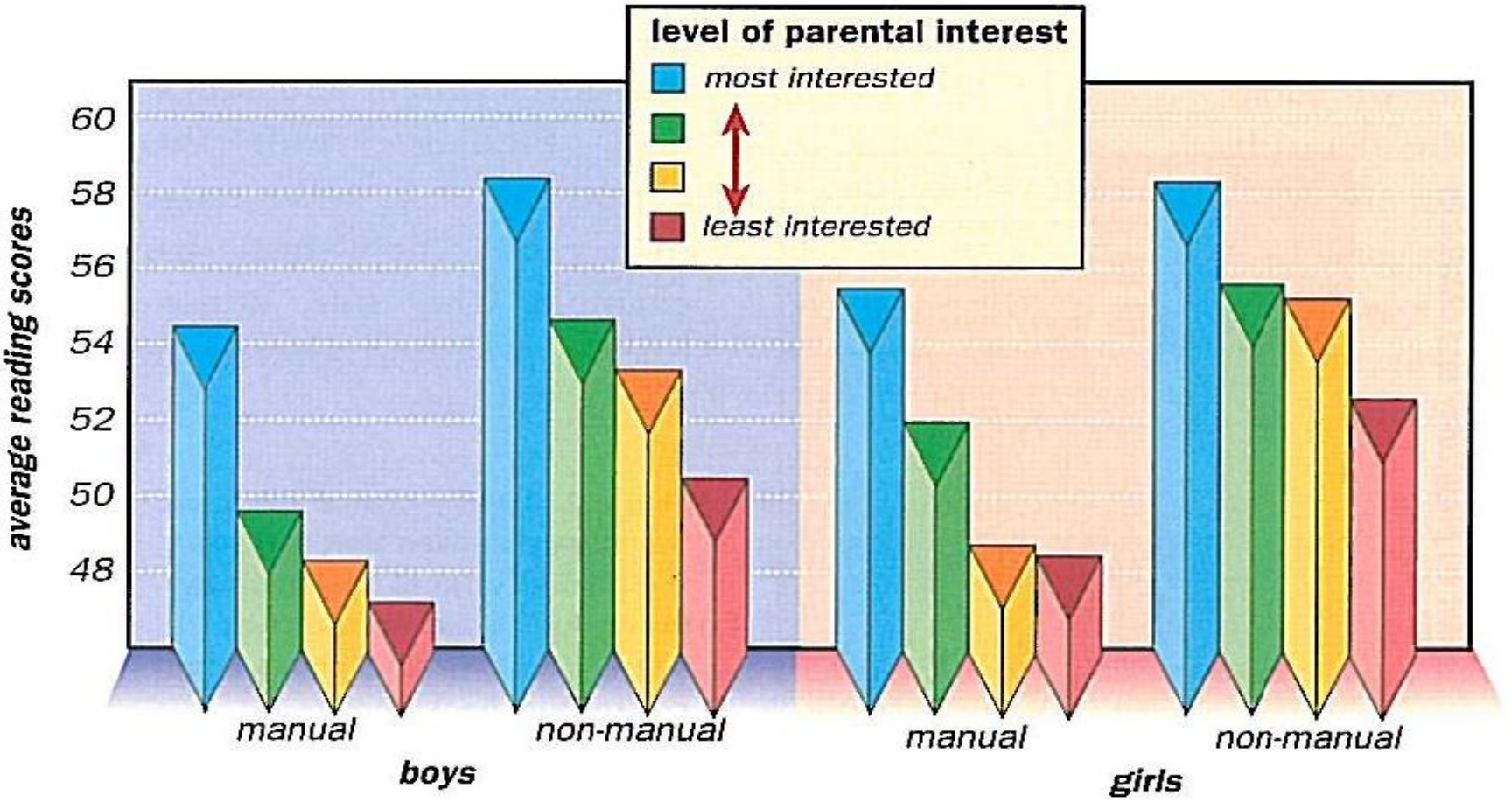


Rawle et al. Transl Psychiat Jan 2018

An updated path model for mental state at age 69



Age 8 reading scores by level of parental interest



Douglas JBL, *The Home and the School*, 1964

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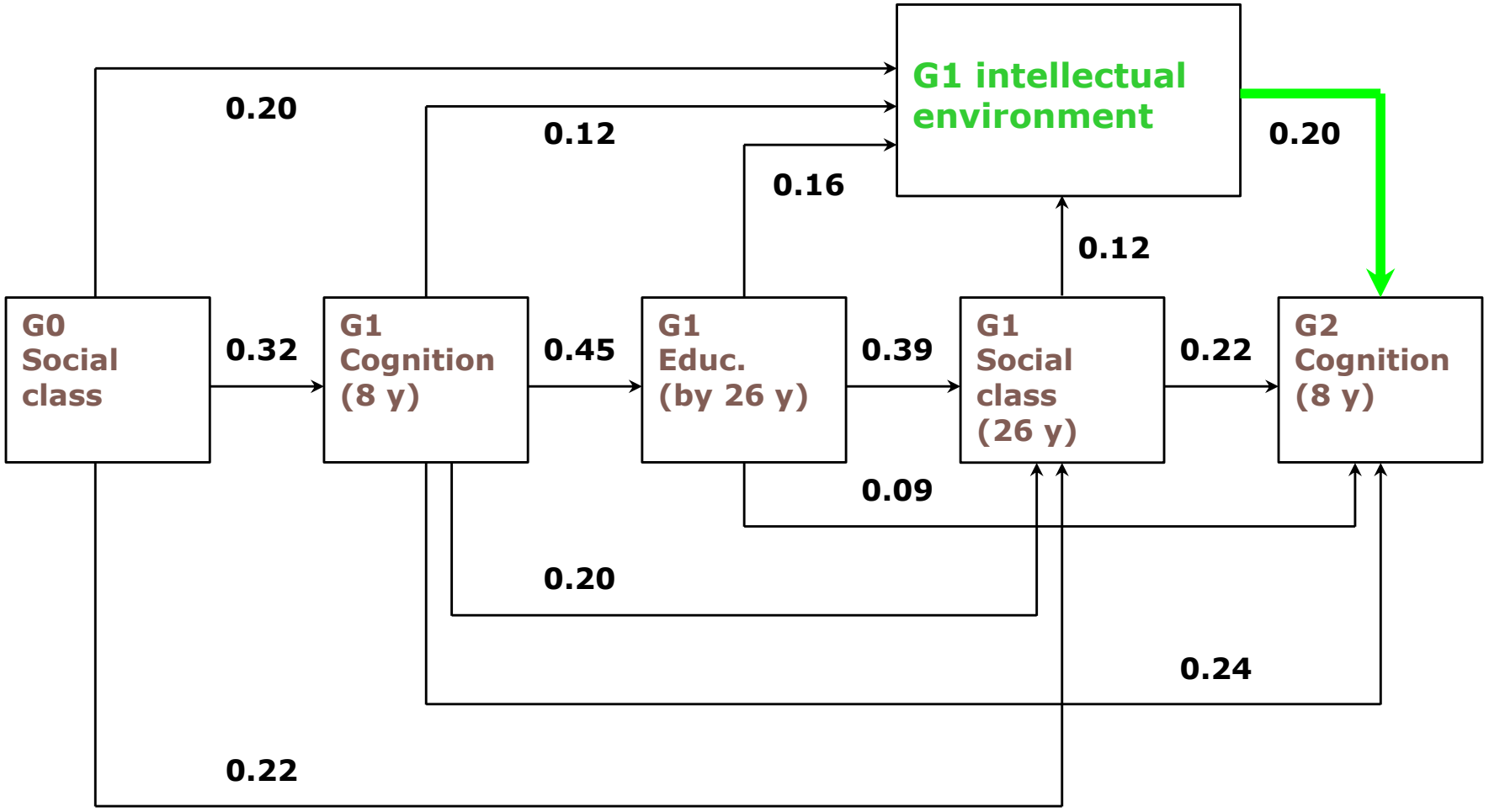
Parenting and the intergenerational transmission of cognition



Byford, Kuh & Richards, International Journal of Epidemiology, 2012

Positive nurturing

Love

Encouragement

Challenge

Parental involvement

"I'm sure you can do better than this."

Skills for life

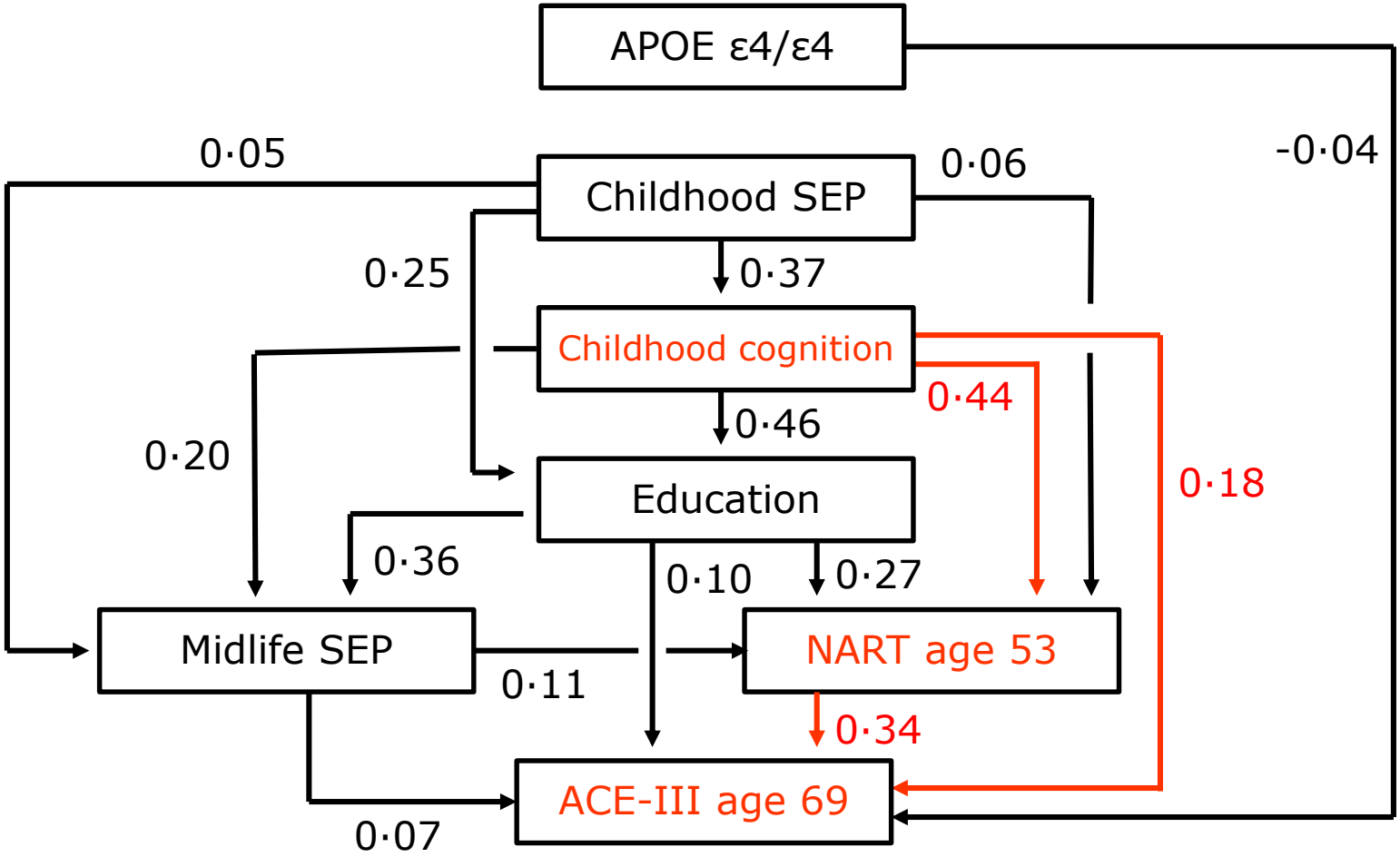
"Cognitive and socioemotional function are intertwined across the life course and, we suggest, fuse to form skills for life supporting self-regulation, competence, and quality of life."

Richards & Hatch, J Gerontology 2011

"... what is needed for optimal cognitive development is a combination of active learning experiences that promote cognitive competence together with a social context in which the style of interaction and relationships promotes self-confidence and an active interest in seeking to learn independently of instruction."

Rutter, J Child Psychol Psychiat 1985

An updated path model for mental state at age 69



The long reach of childhood cognition

Childhood cognition correlates strongly with early adult cognition…

Plassman B, Welsh K, Helms M, Brandt J, Page W, Breitner Journal of Neurology 1995, 45, 1446-50

…midlife cognition (allowing for social class of origin, education, and own social class):

Richards M, Sacker A. Journal of Clinical and Experimental Neuropsychology, 2003, 25, 614-24

…and later life cognition:

Deary IJ, Whalley LJ, Lemmon H, Crawford JR, Starr JM. Intelligence 2000, 28, 49-55

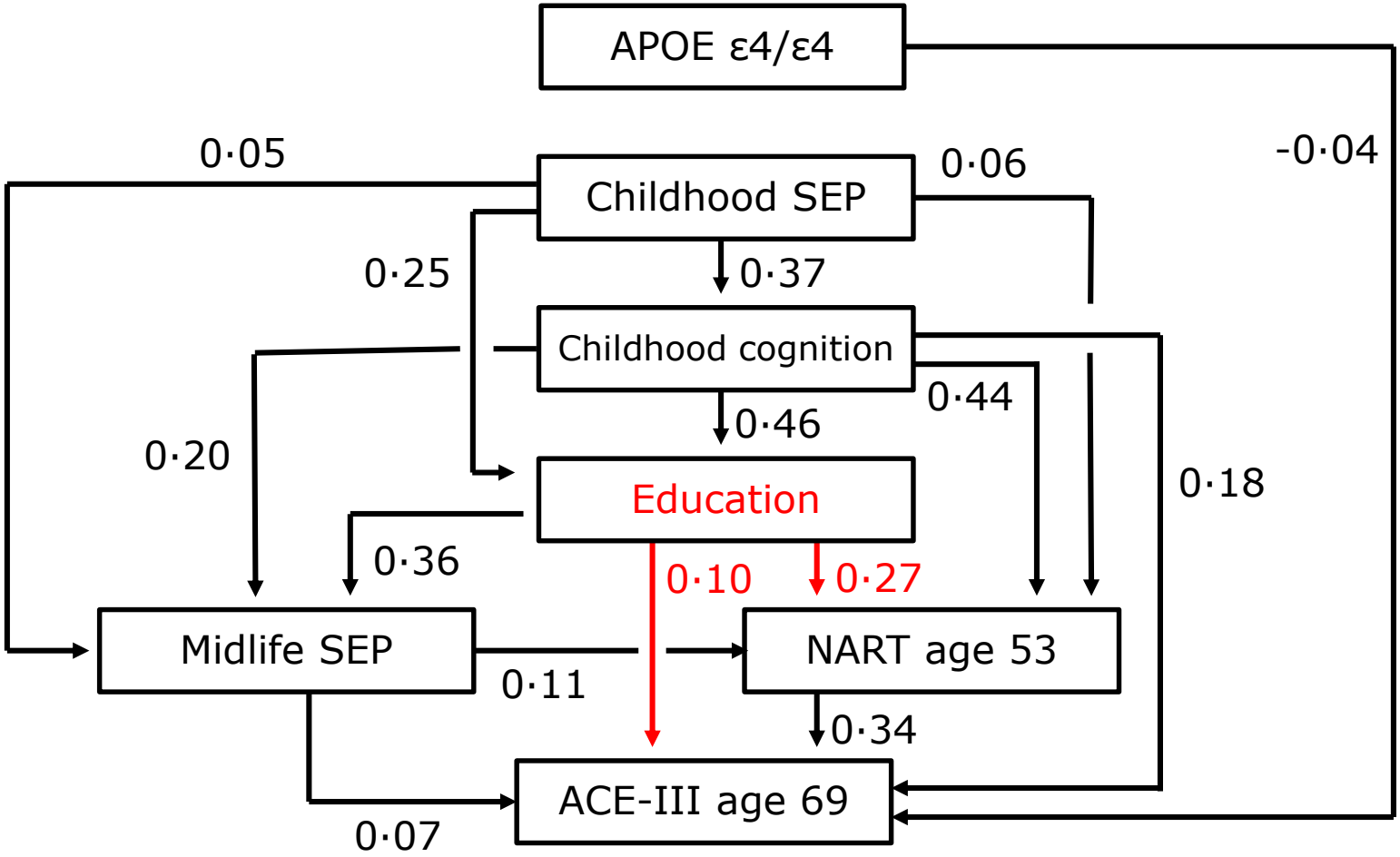
Early cognition and dementia risk

- 93 members of the School Sisters of Notre Dame born before 1917 in the Milwaukee area

- Idea density and grammatical complexity, derived from autobiographies written around age 22 years was a strong predictor of cognitive function and Alzheimer's disease risk in later life (Snowdon et al. JAMA 1996)

- Childhood IQ was associated with late-onset dementia (Whalley et al. Neurology 2000; McGurn et al. Neurology 2008)

An updated path model for mental state at age 69



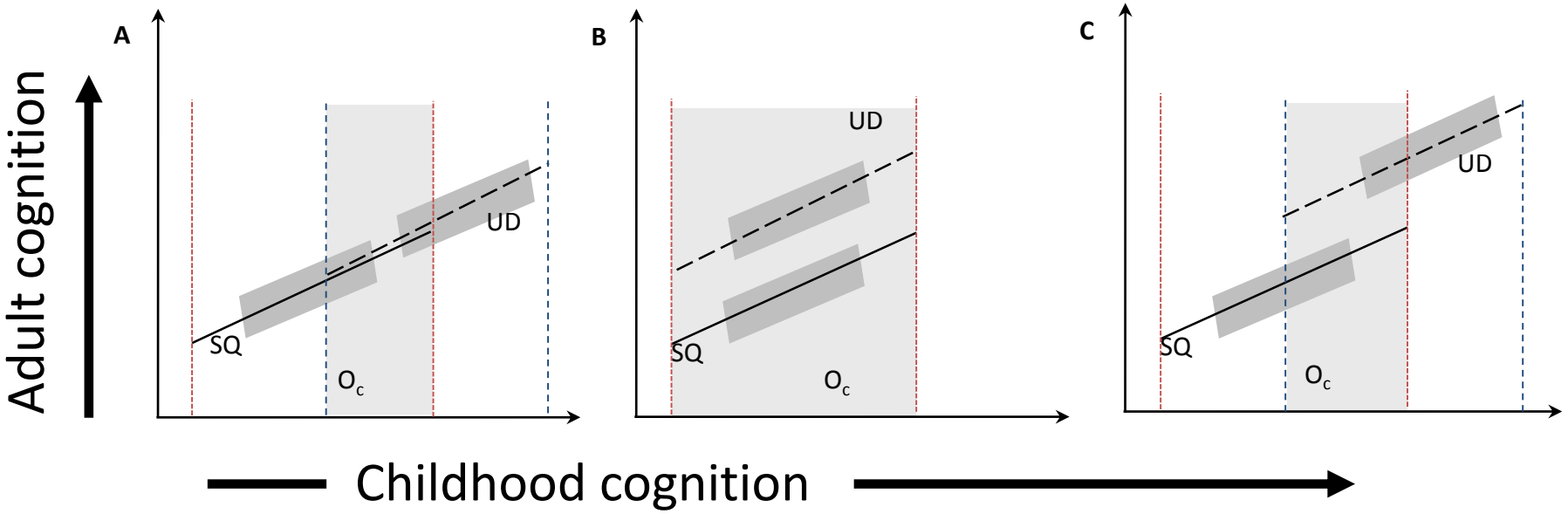
theguardian

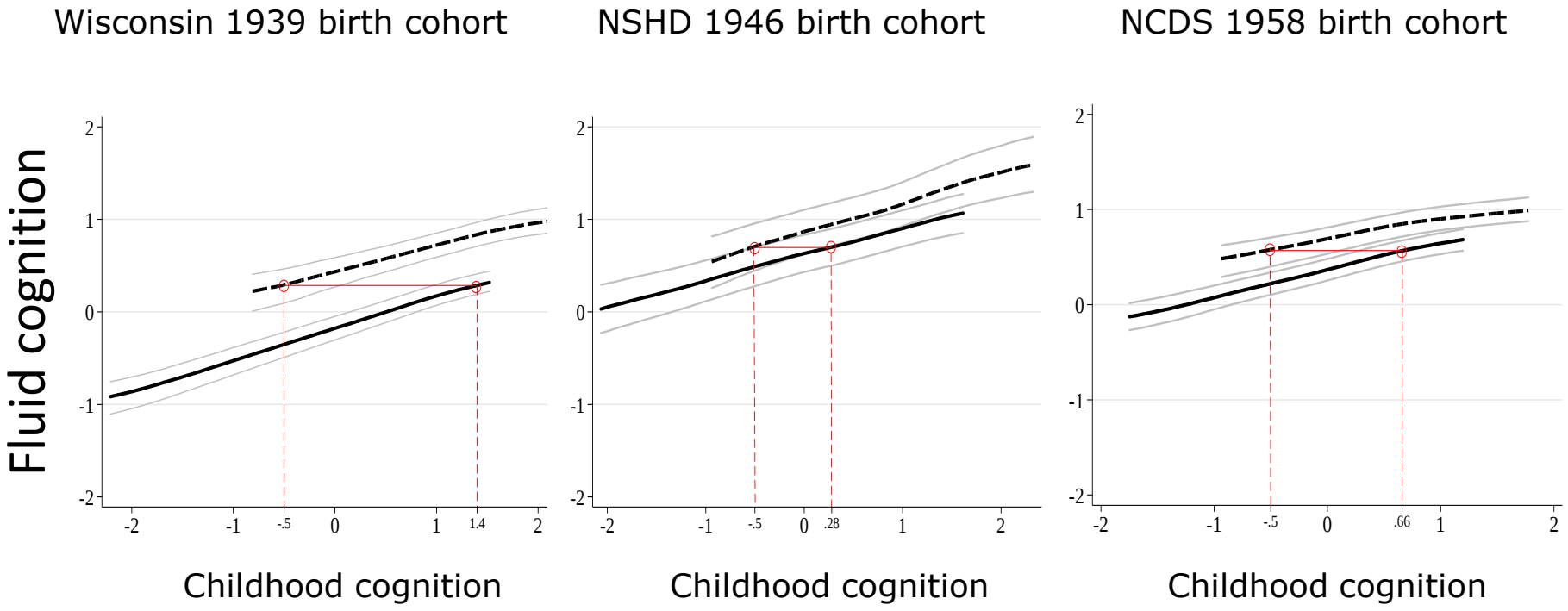
Genetics outweighs teaching, Gove adviser tells his boss

Dominic Cummings' 250-page paper attacks fear of elitism and waste of billions of pounds, and calls for slimmed-down ministry

Patrick Wintour, political editor
The Guardian, Friday 11 October 2013 22.06 BST

Three possibilities

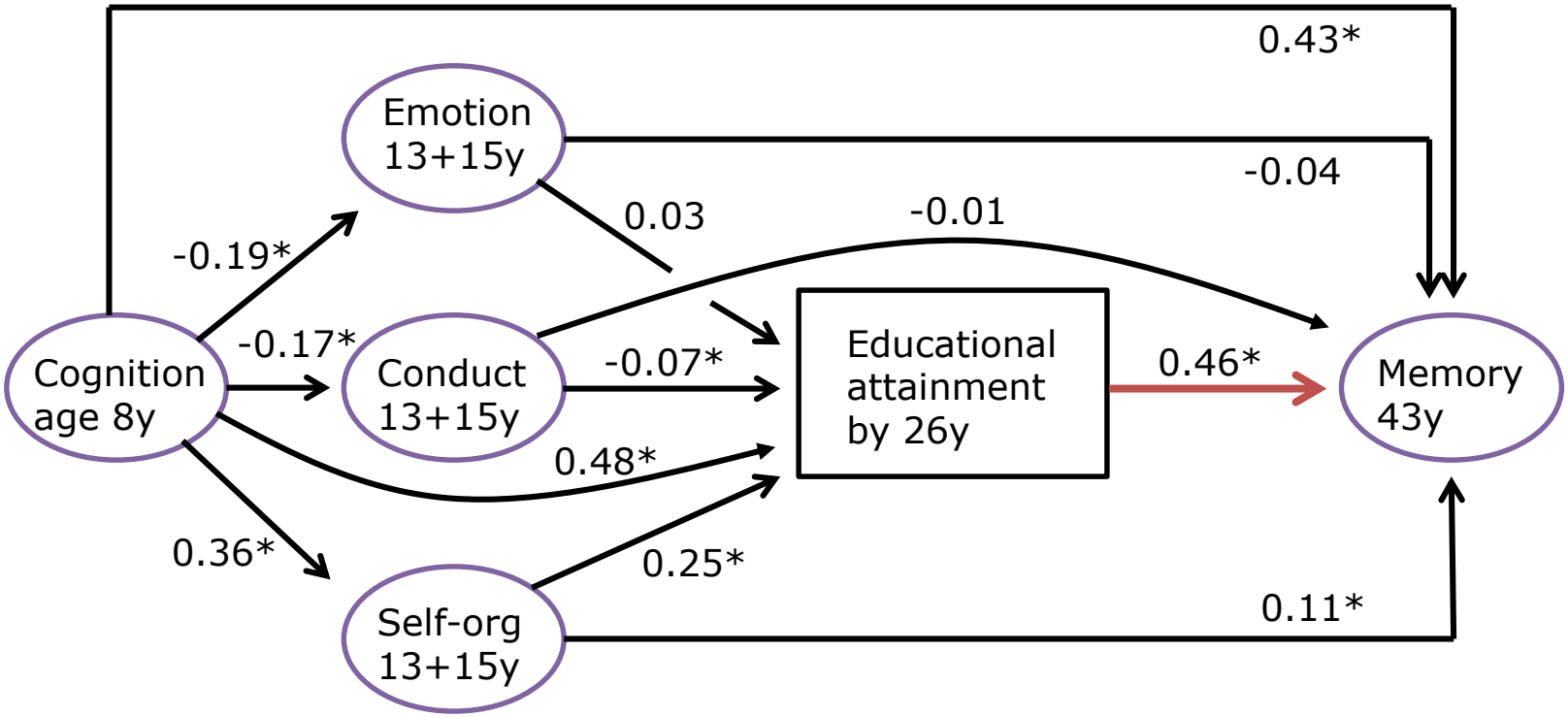




Clouston et al. International Journal of Epidemiology 2012

Self-organisation in NSHD: Teacher ratings at 13 and 15 years

A very hard worker; one with high power of concentration; extremely neat and tidy in class work; seldom or never daydreams in class



Xu et al. Psychology and Aging 2013

Thanks to:

Mai Stafford, Nikhil Sharma, Mark Rawle, Sarah-Naomi James, Daniel Davis and Diana Kuh