Over a Decade of Cross Cohort Work: the IALSA Experience

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Background

- IALSA: Integrative Analysis of Longitudinal Studies of Ageing (initially established in 2005, ongoing with NIH funding)
- 109 studies in the network, 60 of them fully catalogued
- 3 different work packages, including package on cognitive aging and physical health (Piccinin & Muniz-Terrera)
- IALSA aims at generation of strong and robust evidence about scientific findings.
- For this, we tend to use a multi cohort approach for our work

- Studies differ in design (follow up time, separation of data collection waves, cohort differences)
- Numerous tests exist to measure the same cognitive function (ex: verbal fluency, immediate recall, orientation). Test differ either @ item level/completely different test
- Differences in other domains (ex: physical activity scales)
- So, given a research question (ex: is education associated with level or rate of change in memory?), ***how can we go about evaluating whether a result in a specific study replicates, so that we start to believe it's "a thing"?***
- Life is "easier" in some other fields, where IPD, meta analyses techniques have flourished, but we usually deal with heterogeneity in measures that limit our ability to combine data

Example

- Is education associated with rate of change in global cognitive function?
- Cognitive reserve hypothesis: individuals with higher reserve can cope with pathological brain damage for longer
- Education commonly used proxy for reserve
- Numerous studies have evaluated this question . Let’s examine some of them

Table 1. Methods and Findings from Previous Studies of Education and Rate of Change in Mini-Mental State Examination (MMSE)

Publication	Education–cognitive change association?	Education measure	Cognitive measure	Method	Conclusion	*n* at T1	Age	Study length (years)	# waves	Sample	BP age as covariate	Conditioned on baseline performance
Folsher and Wallace (1991a)	(Y) NO	<9, 9–12, >12 years	SPMSQ	Sex-specific repeated measures analysis of variance	Women with less education declined more between T1 and T2 but overall did not have a greater rate of decline	1,953	62+	6	3	Iowa 65+ Rural Health Study	Y	N
Evans et al. (1993)	Y	Years	SPMSQ	Regression of normalized change scores on education and other covariates	Fewer years formal education, greater declines in cognitive function	2,273	65+	3	2	East Boston EPESE	Y	Y
Farmer et al. (1995)	Y	0–9 vs. 10–12 and some college+	MMSE	Logistic regression (3+ point decline in 1 year)	Decline more likely in lower education group with MMSE >23 (not for MMSE =<23).	14,883	18+	1	2	NIMH ECA	Y	Y
Butler, Ashford, and Snowdon (1996)	Y	<Bachelors vs. Bachelors	MMSE	Annualized change; compared top three T1 MMSE categories (20–23, 24–26, 27–30) for two levels of education and two age groups	75–84 years: bachelors, less decline; 85+ years: bachelors, more decline	575	75–102	1.6	2	Nun	Groups*	Y
Christensen, Korten, Jorm, and Henderson (1997)	Y	Years and <10, 10–13, 14+	MMSE	Change scores regressed on predictors	Lower education predictive of decline	617	70+	3.5	2	CLS	Y	Y
Tyketsos, Chen, and Anthony (1999)	Y	0–8 (reference), 9–11, 12, 13–15, 16	MMSE	T3–T2 change scores regressed on predictors	More decline in those with ≤8 years education with and without adjusting for age (group).	1,488	18–75+	2	5	Baltimore ECA	Groups*	Y
Clevarsson and Skoog (2000)	Y	6 vs. >6 years	MMSE	Change score	More decline in nondemented women with less education	102	85	3	2	Gothenburg	NA (single-age sample)	Y
Jacqmin-Gadda et al. (1997)	Y (for SQRT MMSE errors)	none, < primary, primary, high school, university; in education × time analysis: < vs. > high school	*Square root* of MMSE errors	Time-based growth model	Less decline with more education	2,792	65+	5	4	PAQUID	Y	N
Nguyen, Black, Ray, Espino, and Markides (2002)	Y	<5, 5–11, >11	MMSE	Logistic regression	Significant odds ratio for <5 years of education relative to >11 years.	1,759	65+	5	2	Hispanic EPESE	Y	N

Differences in covariates available

Differences in outcomes

Differences in methods

Differences in coding of covariates

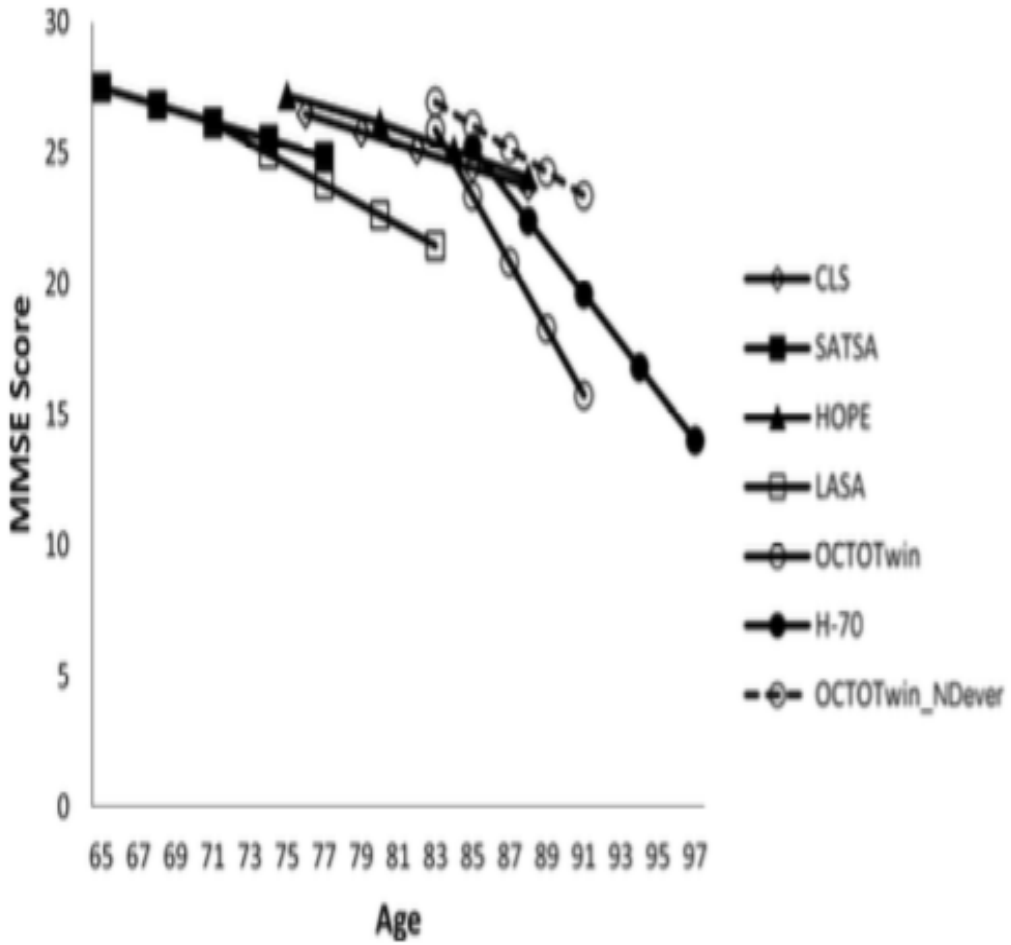
All potential sources of heterogeneity in results reported!

Coordinated Analyses

- We cannot control some sources of heterogeneity (separation of waves, timing of cohort, data available)
- But we can use the same/as similar as possible analytical method in multiple studies
- *Independent* analyses of datasets (no data pooling)
- Permits evaluation of *consistency of patterns* of associations
- Within this framework, we did a coordinated analyses of MMSE scores in 6 longitudinal studies of ageing

How we did it:

- In depth understanding of data from 6 studies
  - SATSA, OCTO & H70 (Sweden), CLS (Australia), LASA (Netherlands), HOPE (Scotland)
  - Education :
    - HOPE :9 years of education was the median value
    - H-70, OCTO-Twin, SATSA: median 6 yrs.
    - LASA : median 6 years of education.
    - CLS: median education of 11 years.
    - Considering the median and range for each study, the approach here was to code education as a continuous variable, with the exception of H-70 (already coded 6 vs. >6 years) and SATSA (with four categories, rescored to match H-70
- Latent growth model adjusted for age (@83 yrs), sex, education



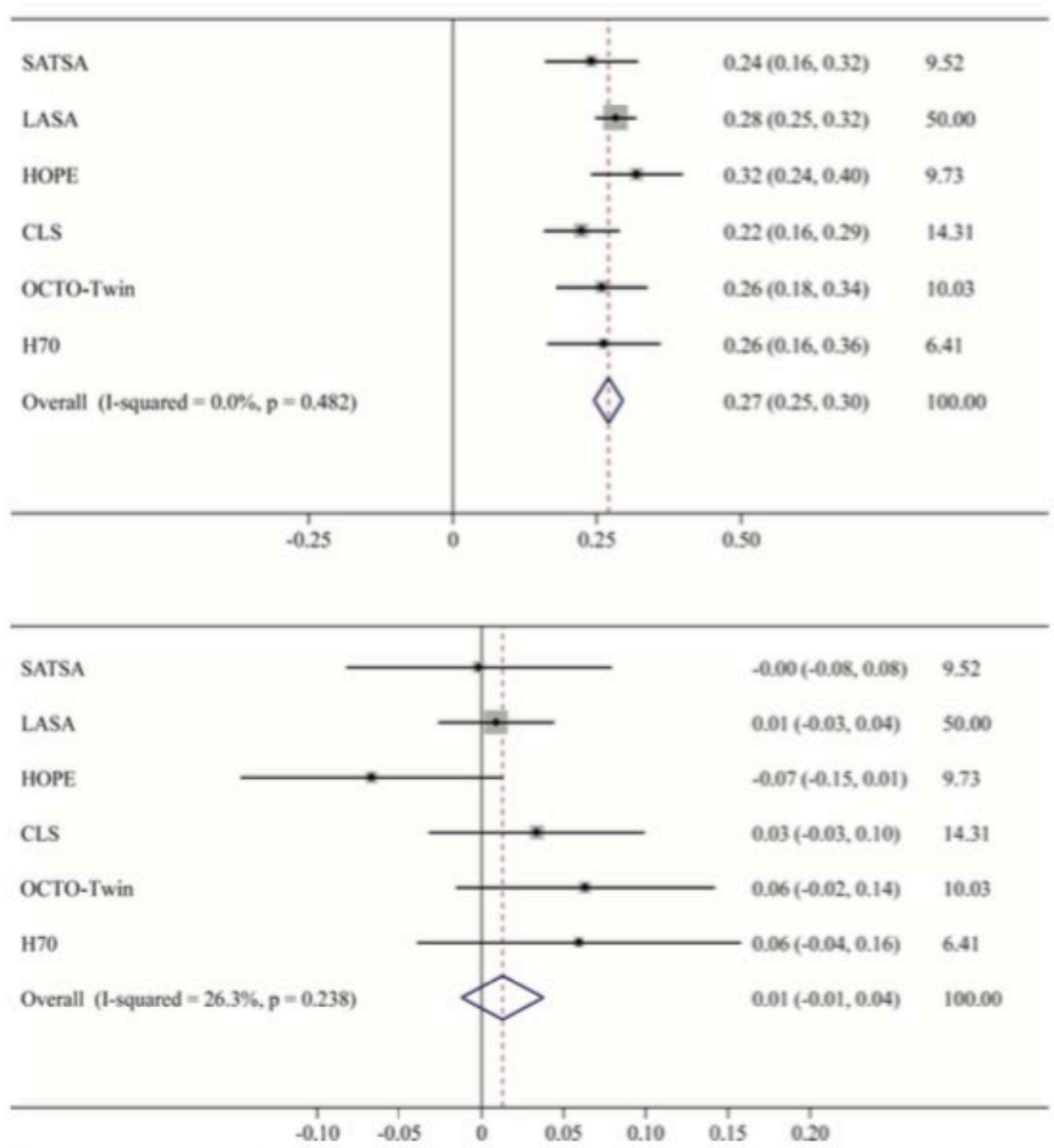


Figure 2. Meta-analysis using estimated age-distributed between-person (BP) differences (education) and within-person (WP) change (education × time) results for six studies. (**Top panel**) Educational attainment intercepts. (**Bottom panel**) Education × Time. *Note*. Estimates have been standardized to account for sample size heterogeneity. Panel 2 uses nondemented estimates for change in educational attainment in the OCTO-Twin study. CLS = Canberra Longitudinal Study; HOPE = Healthy Older Person Edinburgh; H-70 = Gerontological and Geriatric Population Studies in Gothenburg, Sweden; LASA = Longitudinal Aging Study Amsterdam; OCTO-Twin = Origins of Variance in the Oldest-Old; SATSA = Swedish Adoption/Twin Study of Aging.

Table 6. Parameter Estimates (and Standard Errors) from Tobit Growth Curve Models, by Study, for Time-in-Study Metric, with Baseline Age and Education Centered at Study-Specific Median Values

	SATSA	LASA	HOPE	CLS	OCTO-Twin	H-70
Fixed effects						
Intercept	28.195** (.133)	27.437** (.074)	27.844** (.127)	27.075** (.137)	25.897** (.366)	25.207** (.539)
Time	−0.117** (.021)	−0.190** (.013)	−0.159** (.040)	−0.221** (.033)	−1.272** (.125)	−1.119** (.202)
Baseline age	−0.072** (.011)	−0.125** (.007)	−0.129** (.022)	−0.132** (.024)	−0.297** (.062)	n/a
Female	0.022 (.151)	0.396* (.113)	0.311 (.163)	0.467* (.182)	0.258 (.436)	−0.260 (.625)
Education	0.817** (.140)	0.283** (.018)	0.274** (.035)	0.226** (.034)	0.490** (.076)	3.244** (.622)
Time × age	−0.008** (.002)	−0.015** (.001)	−0.022* (.008)	−0.027** (.005)	−0.084** (.023)	n/a
Time × female	−0.077* (.025)	0.004 (.015)	0.027 (.051)	0.025 (.036)	0.144 (.139)	−0.413* (.182)
Time × education	−0.001 (.027)	0.001 (.002)	−0.018 (.011)	0.008 (.008)	0.077* (.027)	0.209 (.177)
Variance components and fit indices						
Intercept	1.796** (.413)	6.139** (.517)	0.877* (.368)	3.798** (.802)	22.070** (3.327)	32.226** (5.602)
Slope	0.051** (.014)	0.039** (.007)	0.092 (.060)	0.077** (.023)	1.244** (.194)	1.115** (.195)
Cov(IS)	0.018 (.054)	0.074 (.051)	0.164 (.090)	0.058 (.103)	3.005** (.561)	3.617** (.806)
Residual	2.797** (.329)	4.103** (.152)	3.166** (.336)	3.449** (.309)	12.306** (1.061)	8.766** (.961)
AIC	9041.668	44259.453	3933.143	9781.348	11070.583	5601.338
BIC	9109.791	44345.677	6016.708	9848.785	11137.643	5649.647
Variance components and fit indices for standard growth curve models						
Intercept	1.521** (.389)	5.586** (.490)	0.695* (.279)	3.792** (.798)	18.674** (2.922)	26.247** (4.786)
Slope	0.054** (.015)	0.040** (.007)	0.100 (.056)	0.075** (.023)	1.293** (.192)	1.250** (.213)
Residual	2.166** (.273)	3.166** (.121)	2.117** (.251)	3.434** (.307)	9.398** (.846)	7.283** (.792)
AIC	9276.931	45949.942	6217.217	9781.371	11875.847	5858.704
BIC	9345.054	46036.166	6280.782	9848.808	11942.907	5907.013

Notes. AIC = Akaike information criterion; BIC = Bayesian information criterion; CLS = Canberra Longitudinal Study (median age = 76 years, education = 11 years); HOPE = Healthy Older Person Edinburgh study (median age = 76 years, education = 10 years); H-70 = Gerontological and Geriatric Population Studies (age = 85 years, education dichotomized ≤6 vs. >6 years); LASA = Longitudinal Aging Study Amsterdam (median age = 70 years, education = 9 years); n/a = not applicable; OCTO-Twin = Origins of Variance in the Oldest-Old (median age = 83 years, education = 6 years); SATSA = Swedish Adoption/Twin Study of Aging (median age = 64 years, education dichotomized ≤6 vs. >6 years).

*$p < .05$. **$p \leq .001$.

But in this case *we had* access to data from most studies

- That is not always the case, which results in multiple challenges
  - Data access- several groups do not/cannot share their data
  - When data sharing ok, data transfer agreements can take a long time

We came up with a solution:

- Organisation of workshops
  - PIs contacted and asked to nominate early career researcher (ECR)
  - ECR analyse data from study they are affiliated to
    - Win-win situation (training+ publication + in depth knowledge of data by analyst)
    - Data not shared
- Joint publication

Example 2

Question:

Is education associated with transitions across an individual's entire cognitive journey & death?

Steps:

- Identified suitable studies
- Contacted PIs and invited early career researchers (ECR)

- Got together in Amsterdam
- Trained ECR & discussed analyses
- TCs as follow up after workshop
- **VOILA!!**

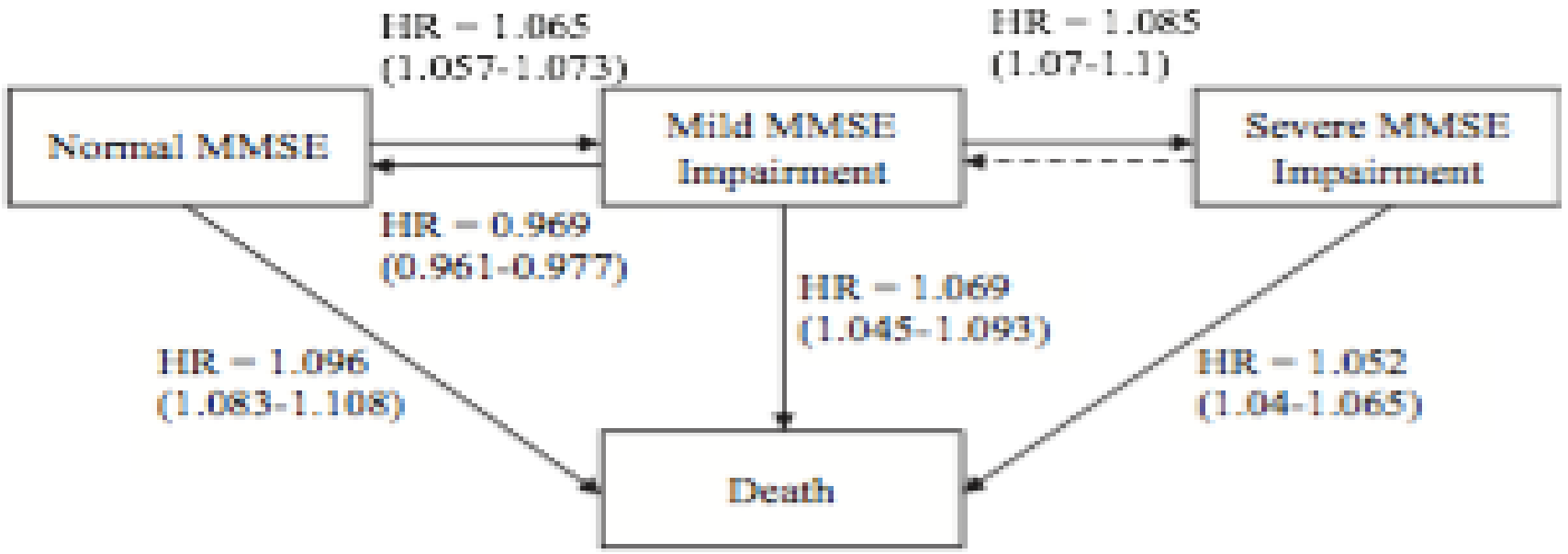


Fig. 2. Four-state model which illustrates the effect of age on cognitive functioning including pooled HRs (95% confidence intervals). The dotted line represents the observed model which is assumed to be a misclassification of the true state. Abbreviations: HR, hazard ratio; MMSE, Mini-Mental State Examination.

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Featured Article

Transitions across cognitive states and death among older adults in relation to education: A multistate survival model using data from six longitudinal studies

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Table 2
Hazard ratio and 95% confidence intervals for the effect of covariates on transitions of older adults through the different states of cognitive functioning

	OCTO-Twin (N = 694)	LASA (N = 2570)	Whitehall (N = 1396)	H70 (N = 898)	LBC1921 (N = 550)	MAP (N = 1449)
Transition	Hazard ratios (95% CIs)					
Age						
State 1–state 2	1.12 (1.06, 1.17)*	1.05 (1.04, 1.06)*	1.02 (0.95, 1.09)	1.09 (0.98, 1.20)	1.14 (1.05, 1.24)*	1.08 (1.07, 1.09)*
State 1–state 4	1.16 (1.09, 1.23)*	1.09 (1.07, 1.10)*	1.14 (1.06, 1.22)*	1.08 (0.99, 1.18)	1.18 (1.10, 1.27)*	1.10 (1.07, 1.13)*
State 2–state 1	0.96 (0.88, 1.04)	0.96 (0.95, 0.97)*	0.91 (0.86, 0.96)*	1.16 (1.03, 1.30)*	0.99 (0.87, 1.12)	0.98 (0.96, 0.99)*
State 2–state 3	1.08 (1.04, 1.13)*	1.11 (1.09, 1.13)*	1.15 (0.98, 1.36)	1.13 (1.01, 1.27)*	1.22 (0.95, 1.57)	1.05 (1.02, 1.07)*
State 2–state 4	1.11 (0.98, 1.27)	1.06 (1.03, 1.08)*	1.12 (0.92, 1.36)	1.16 (1.00, 1.36)*	1.19 (0.99, 1.44)	1.11 (1.04, 1.18)*
State 3–state 4	1.05 (1.02, 1.07)*	1.05 (1.04, 1.07)*	—	1.00 (0.92, 1.10)	1.16 (1.02, 1.31)*	1.06 (1.03, 1.09)*
Sex						
State 1–state 2	1.45 (1.07, 1.94)*	1.45 (1.26, 1.67)*	0.91 (0.62, 1.34)	1.02 (0.70, 1.49)	1.12 (0.63, 1.99)	1.36 (1.17, 1.58)*
State 1–state 4	1.45 (0.92, 2.29)	1.80 (1.44, 2.24)*	1.00 (0.61, 1.65)	1.98 (1.03, 3.82)*	0.51 (0.26, 0.99)*	1.44 (0.94, 2.20)
State 2–state 3	1.42 (1.02, 1.97)*	1.04 (0.77, 1.39)	2.72 (0.68, 10.91)	1.21 (0.66, 2.22)	2.30 (0.54, 9.79)	0.87 (0.65, 1.17)
State 2–state 4	0.61 (0.08, 4.86)	1.95 (1.33, 2.84)*	—	2.89 (0.97, 8.66)	1.25 (0.24, 6.60)	1.74 (0.94, 3.25)
State 3–state 4	1.60 (1.25, 2.03)*	1.27 (1.02, 1.58)*	—	1.50 (0.85, 2.65)	1.05 (0.47, 2.37)	1.30 (0.98, 1.72)
Medium versus low education						
State 1–state 2	0.46 (0.22, 0.96)*	0.53 (0.45, 0.63)*	0.51 (0.26, 1.03)	0.88 (0.53, 1.46)	0.70 (0.40, 1.22)	0.50 (0.30, 0.83)*
State 1–state 4	1.94 (1.09, 3.43)*	0.94 (0.73, 1.20)	—	0.94 (0.30, 2.93)	—	1.31 (0.26, 6.66)
State 2–state 3	1.39 (0.65, 2.96)	0.92 (0.62, 1.36)	1.20 (0.21, 6.72)	1.83 (0.85, 3.91)	0.87 (0.27, 2.83)	2.39 (0.99, 5.80)
State 2–state 4	—	1.04 (0.66, 1.64)	—	0.43 (0.03, 5.55)	—	0.84 (0.04, 15.75)
State 3–state 4	0.87 (0.48, 1.59)	1.33 (0.97, 1.83)	—	1.12 (0.52, 2.39)	—	1.22 (0.54, 2.75)
High versus low education						
State 1–state 2	0.48 (0.25, 0.90)*	0.40 (0.32, 0.50)*	0.48 (0.26, 0.91)*	0.95 (0.57, 1.58)	0.68 (0.37, 1.26)	0.40 (0.29, 0.54)*
State 1–state 4	1.44 (0.82, 2.51)	0.92 (0.70, 1.20)	—	1.11 (0.49, 2.50)	—	0.82 (0.21, 3.15)
State 2–state 3	1.42 (0.65, 3.12)	1.09 (0.67, 1.77)	0.33 (0.06, 1.84)	1.55 (0.66, 3.66)	0.39 (0.09, 1.80)	1.33 (0.66, 2.66)
State 2–state 4	—	0.97 (0.51, 1.84)	—	0.36 (0.04, 3.19)	—	1.13 (0.25, 4.97)
State 3–state 4	1.56 (0.84, 2.91)	1.15 (0.76, 1.72)	—	0.80 (0.32, 1.98)	—	0.77 (0.43, 1.39)
Socioeconomic status						
State 1–state 2	0.94 (0.77, 1.15)	0.79 (0.73, 0.86)*	0.95 (0.74, 1.21)	0.69 (0.51, 0.92)*	0.93 (0.61, 1.44)	0.90 (0.82, 0.99)*
State 2–state 3	0.88 (0.70, 1.11)	0.84 (0.72, 1.00)*	0.90 (0.45, 1.76)	0.70 (0.40, 1.22)	0.69 (0.29, 1.64)	0.95 (0.79, 1.13)

Abbreviations: OCTO-Twin, Origins of Variance in the Oldest-Old; LASA, Longitudinal Aging Study Amsterdam; LBC, Lothian Birth Cohort 1921; MAP, Memory and Aging Project; CI, confidence interval.

NOTE. state 1 = normal MMSE; state 2 = mild MMSE impairment; state 3 = severe MMSE impairment, state 4 = death.

*Significant hazard ratio.

Challenges

- Time to publication- because each paper involves analysis of multiple cohorts, it takes longer to complete a paper
- Cultural shift required (from evaluators, editors, PIs). Longer papers. We had 9 reviewers!
- Full coordinated analysis not always possible (MSM leisure activities, gait speed)
- We suggest subgroup analyses & sensitivity analyses (adding to length of paper) though much more thorough work
- Requires longer term commitment & funding

Advantages

- Allows evaluation of replication & produces strong evidence
- Avoids 2 step approach (analytical harmonisation that may be “noisy” + data pooling)
- Smooths out analytical differences, hence reducing potential sources of conflicting results
- Avoid lengthy and tiring data transfer agreements
- Our meetings involve training & networking opportunities for ECR
- Win win situation!