

RESEARCH ARTICLE

Studying at university in later life slows cognitive decline: A long-term prospective study

Aidan D. Bindoff¹ | Mathew J. Summers² | Edward Hill¹ | Jane Alty¹ | James C. Vickers^{1,3}

¹ Wicking Dementia Research & Education Centre, College of Health and Medicine, University of Tasmania, Hobart, Tasmania, Australia

² School of Health and Behavioural Sciences, University of the Sunshine Coast, Sippy Downs, Queensland, Australia

³ School of Medicine, College of Health and Medicine, University of Tasmania, Hobart, Tasmania, Australia

Correspondence

Aidan D. Bindoff, Wicking Dementia Research & Education Centre, College of Health and Medicine, University of Tasmania, Private Bag 143, Hobart, TASMANIA 7001, Australia.
Email: aidan.bindoff@utas.edu.au

Abstract

Introduction: Declining cognition in later life is associated with loss of independence and quality of life. This decline in cognition may potentially be reduced or reversed through engaging in cognitively stimulating activities. This study examined the potential for university attendance in later life to enhance cognitive function in older adults.

Methods: Cognitively unimpaired adults ($n = 485$, 69% female, median age 60 years) were given the opportunity to undertake free university study. Repeated neurocognitive assessment was performed over 7 years.

Results: Participants in the university education group ($n = 383$) improved $z = .02$ SD (.01, .03) per year of the study compared to controls ($P = .001$; averaged across a battery of cognitive tests). The largest improvements were observed on tests of language and verbal learning, memory, and episodic memory.

Discussion: Later-life university study was associated with improved cognitive trajectories. Later-life education may preserve cognitive function, specifically for functions associated with communication, social interaction, and maintaining independence.

KEYWORDS

age-related cognitive decline, cognitive aging, cognitive reserve, dementia prevention, lifespan cognitive reserve

1 | BACKGROUND

“Living well” into the later years of life is dependent not only on physical and mental health, but also on cognitive health. Social engagement and independence are closely tied to a capacity to communicate, make decisions, understand new information, remember past events, and form new memories. As populations age, cognitive functions display age-related declines across the domains of attention, concentration, and processing speed, and the ability to remember events or details. These functions are important to maintain health and well-being in later life.^{1,2}

There is a well-established evidence base for the association between early life education, career attainment, and cognitively stimulating leisure activities with preserved later-life cognitive function^{3,4} and delayed or reduced cognitive symptoms of dementia.^{5,6} The Lancet International Commission on Dementia Prevention and Care concluded that low educational attainment accounted for 7% of the population attributable fraction of global dementia risk.⁷ A proposed mechanism for the protective effect of education is cognitive reserve (CR)⁵—the compensatory ability of the brain to maintain function despite advancing brain pathology. Education and other cognitively stimulating experiences are thought to build a reserve of cognitive capacity.

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The direct relationship between early life education and later-life cognitive function may be confounded by intelligence quotient (IQ; people who perform well on cognitive tests tend to stay in school longer), and barriers to access including socio-economic disadvantage and socio-cultural factors.⁸ The same advantages that are associated with higher education are also associated with other health outcomes.⁹ Early life education may advance life-long cognitively stimulating work and leisure activity, thereby contributing to the preservation of cognitive function, reserve against the insults of pathology, and brain maintenance through neuroplasticity.¹⁰ These effects may be cumulative or interdependent, so it is unclear what benefit education confers independently. Later-life education, relatively free of expectations around work or career advancement, socio-economic opportunity, and provided with fewer barriers to entry (through subsidized fees and relaxed entry criteria), may provide a conduit to further understanding of potential benefits of education in preserving cognitive function in later life.

Interventions aimed at assessing the benefit of later-life cognitively stimulating activities such as brain-training and exercises specific to building targeted cognitive functions have provided mixed evidence of their effectiveness in slowing cognitive decline and delaying the cognitive symptoms of dementia. Studies fall broadly into two categories—single-domain cognitive training interventions and multi-domain trials that may include cardiovascular, dietary, hypertension, or other interventions aimed at improving modifiable risk factors.

Single-domain cognitive training interventions to date have had mixed results, but have been of shorter-duration (5 to 6 weeks),^{11,12} and initial post-intervention gains have not been sustained at follow-up.¹³ Multidomain trials have been of longer duration (up to 2 years)¹⁴ but have focused largely on older cohorts.¹⁵ It is difficult to attribute a benefit specifically to cognitive training or education in multidomain trial designs because the cognitive training occurs concurrently with other interventions.

The Tasmanian Healthy Brain Project (THBP) is an ongoing longitudinal intervention study of cognitively healthy individuals over 50 with a self-selected intervention group who participated in university education. The aim of the present study was to evaluate differences in cognitive trajectories between participants in intervention and comparison groups on cognitive test scores across the domains of language processing, executive function, episodic memory, and working memory. This study extends earlier published work from the THBP,^{12,16–18} covering a longer duration (7 years compared to 3 years). Because cognitive benefits of education may be age- and dose-dependent, we investigated whether the putative benefits of later-life education diminished for older participants, and whether benefits increase in proportion to academic load.

2 | METHODS

2.1 | Study design and participants

The Tasmanian Healthy Brain Project (THBP) is a non-randomized prospective, longitudinal cohort study investigating the effect of

RESEARCH IN CONTEXT

- 1. Systematic Review:** An extensive search for research literature on cognitive intervention studies for age-related cognitive decline and dementia prevention identified two broad classes of research: single-domain cognitive interventions, which were of short duration (5 to 6 weeks) and multi-domain (eg, incorporating dietary interventions) with longer follow-up (2 to 3 years). Both types had mixed results. It remains unclear if later-life education slows age-related cognitive decline.
- 2. Interpretation:** We found that later-life education slowed cognitive decline and improved cognitive function, especially verbal memory, verbal fluency, and episodic memory. Older participants benefited most from the intervention. This study is a world-first longitudinal intervention study examining the effects of later-life university education in an aging cohort.
- 3. Future Directions:** These findings suggest that later-life education improves cognitive trajectories in adults aged 50 and older. Randomized controlled trials may be justified to confirm the causal effect of education on cognitive outcomes and incidence of dementia.

HIGHLIGHTS

- Cognitively unimpaired adults 50 and older were given the opportunity to undertake fee-waived university-level study. Participants in later-life education and comparison groups were followed with repeated neurocognitive assessment over 7 years.
- Participants in the later-life education group had improved cognitive trajectories relative to controls on tests of language and verbal learning, verbal memory, and episodic memory.
- Older participants benefited from later-life education at least as much as their younger peers.
- Later-life education may slow age-related cognitive decline, particularly for functions associated with communication, social interaction, and maintaining independence.

university-level education on age-related cognitive decline and dementia risk in adults ages 50 to 79 at baseline entry into the study. The design and methods of the THBP have been described in detail previously.^{19,20} Participants were unpaid volunteers recruited through print, television advertising, radio, and community information presentations. Participants were screened to exclude conditions

independently associated with cognitive impairment. Baseline assessments beginning in 2011 were completed on 566 participants. To date, 156 participants (27.6%) have withdrawn from the THBP. The majority of withdrawing participants report factors unrelated to the study: 22% relocated, 13% unable to recontact, 9% too busy, 10% medical diagnosis, 6% deceased, 3% work commitments, 2% family issues, 28% provided no reason, and 7% found the assessments too stressful. Medical diagnoses were predominantly cancer and neurological disorders. No participants stated that dementia diagnosis was their reason for withdrawal. Of the 566 enrollments, 438 participants chose to join the intervention group and undertake university study in a course of their choosing. For the purposes of this study, which is to assess the association between later-life education and cognitive trajectories rather than an assessment of fee-waived education as an intervention, we included any participant in the intervention group who completed at least one unit of study. We excluded participants in post-graduate courses because (1) it was not possible to determine an equivalent academic load and (2) there was a high likelihood of recent (but not necessarily post-baseline or over 50) university-level study. Furthermore, following scrutiny of university records, some participants in the comparison group had undertaken university study after the study began and were excluded from this analysis. These criteria resulted in exclusion of $n = 55$ participants in the intervention group and $n = 26$ participants in the comparison group (Table 1).

2.2 | Procedures

Assessments were completed annually on a battery of cognitive tests (outlined in Table 2) for the first 36 months, and then every 2 years up to 7 years from baseline (six assessments in total have been included in this study). Tests were conducted using pen and paper or computer, as appropriate, under the supervision of trained research assistants in Hobart and Launceston, Tasmania, and verified by a clinical neuropsychologist (MJS) who provided feedback to participants at each assessment phase.

Written informed consent was obtained from all participants at each assessment. Approval was granted by the University of Tasmania Human Research Ethics Committee (H11070/H18265) in accordance with the National Statement on Ethical Conduct in Human Research (National Health and Medical Research Council of Australia).

2.3 | Outcome measures

A subset of cognitive tests from the full THBP battery was chosen for this study based on sensitivity to early cognitive decline across a range of functional cognitive domains. These are outlined in Table 2. Raw test scores (ie, not adjusted using age and gender normatives) were standardized to z-scores using the formula $\hat{z}_{it} = \frac{y_{it} - \bar{y}_t}{SD_t}$, where y_{it} is the i th score for cognitive test instrument t and \bar{y}_t and SD_t are the mean and standard deviation for cognitive test instrument t . This puts scores

TABLE 1 Participant characteristics at baseline, including full-scale intelligence quotient (IQ) estimated using Wechsler Test of Adult Reading (WTAR-FSIQ), early life education, and a socio-behavioral proxy of cognitive reserve which is a composite of early life education, WTAR-FSIQ, and items from the lifetime experience questionnaire including career attainment and cognitively stimulating leisure activities

	Comparison (n = 102)	Intervention (n = 383)
Age		
Mean (SD)	63.2 (6.7)	59.6 (6.6)
Median [Q1, Q3]	64.0 [58.0, 68.0]	59.0 [54.0, 64.0]
Gender		
Female	66 (64.7%)	269 (70.2%)
Male	36 (35.3%)	114 (29.8%)
Academic course load (% of 1-year FTE load) ^a		
Mean (SD)	-	145 (123)
Median [Q1, Q3]	-	113 [50, 206]
WTAR-FSIQ ^b		
Mean (SD)	112 (4.9)	112 (5.7)
Median [Q1, Q3]	114 [109, 116]	114 [110, 116]
Early life education (years)		
Mean (SD)	11.0 (1.2)	11.3 (1.0)
Median [Q1, Q3]	12.0 [10.0, 12.0]	12.0 [10.0, 12.0]
Prior cognitive reserve (z)		
Mean (SD)	-0.17 (1.05)	0.04 (0.96)
Median [Q1, Q3]	0.02 [-0.76, 0.57]	0.05 [-0.48, 0.73]

^aCumulative from baseline to 2019; FTE: full-time or equivalent. ^bWechsler Test of Adult Reading, estimated full-scale intelligence quotient and memory.

from each test instrument on a comparable scale. Trail-making (TMT) and Stroop tests were first \log_{10} -transformed and reversed, and paired associates learning (PAL te6) scores were transformed using the formula $\log_e((score_{max} + 1)/(score_i + 1))$ to improve the normality of residuals and correct sign inconsistencies across instruments.

2.4 | Covariates

The benefit of later-life education is potentially confounded by early life education and other cognitively stimulating activities, so a socio-behavioral proxy of prior (baseline) CR was included as a covariate. The Wechsler Test of Adult Reading (WTAR-FSIQ)²¹ and the Lifetime Experience Questionnaire (LEQ)¹⁰ were administered at baseline. The LEQ assesses participant educational and occupational attainment, along with cognitively stimulating and neuroprotective leisure activities. Weighted scores for items loading on a principal component across LEQ and WTAR-FSIQ were summed using the formula below,

TABLE 2 Sub-set of THBP cognitive test battery¹⁹ assessed in this study

Label	Instrument	Cognitive function/s assessed
BNT	Boston Naming Test	Verbal confrontation naming; language fluency
COWAT	Controlled Oral Word Association Test	Letter verbal fluency; verbal executive function
LM I & II	Logical Memory I & II	Immediate and delayed recall of verbal prose passages; verbal episodic memory
PAL ftm	Paired Associates Learning (first trial memory score)	Immediate recall of visual information; visual episodic memory
PAL te6	Paired Associates Learning (total errors, six shapes)	Recall of visual information on six shapes trial; visual episodic memory recall
RAVLT rcl	Rey Auditory Verbal Learning Test (recall)	Immediate recall of verbal word lists; verbal episodic memory recall
RAVLT tot	Rey Auditory Verbal Learning Test (total)	Learning of verbal word lists; verbal episodic learning capacity
RCFT	Rey Complex Figure Test	Immediate recall of complex geometric design; visual episodic memory recall
RVP-A	Rapid Visual Information Processing (A)	Visual sustained attention and signal detection sensitivity; visual executive function
SSP length	Spatial span (length)	Visual immediate memory span; visual short-term memory capacity
STROOP C time	Stroop color (time)	Verbal information processing speed and impulse control; executive function
SWM be	Spatial working memory	Visual working memory capacity
TMT-B	Trail Making Test (B)	Visuo-motor information processing speed; executive function
WAIS comp	Wechsler Adult Intelligence Scale, 3rd edition (comprehension subtest)	Capacity to use language to express ideas and understand verbal communication; language capacity
WAIS ds	Wechsler Adult Intelligence Scale, 3rd edition (digit span subtest)	Verbal immediate memory span; verbal short-term memory capacity
WAIS Ins	Wechsler Adult Intelligence Scale, 3rd edition (letter-number sequence subtest)	Verbal working memory capacity
WAIS voc	Wechsler Adult Intelligence Scale, 3rd edition (vocabulary subtest)	Word recognition and capacity to define words; language capacity

following a previously described protocol,²⁰

$$\begin{aligned} \widehat{\text{Prior CR}} = & .370(\text{WTAR} - \text{FSIQz}) + .408(\text{Years of early life education}) \\ & + .567(\text{LEQ young adult specific}) \\ & + .565(\text{LEQ young adult nonspecific}) \\ & + 1.004(\text{LEQ midlife specific}) \\ & + .630(\text{LEQ midlife nonspecific}) + .875(\text{LEQ midlife bonus}) \end{aligned}$$

There is evidence that CR moderates the steepness of cognitive aging trajectories (although this is contested: see²² and²³) and retest practice effects,²⁴ so we included the prior CR variable as a time-varying covariate.

Total university study completed before the sixth assessment was ascertained from academic records. Each unit of undergraduate study was measured as a proportion of 1 year full-time or equivalent (FTE) study load, where a typical unit is weighted at 12.5% of a 1-year FTE study load.

2.5 | Statistical methods

All data-handling and statistical analysis were conducted in the R (v3.6) statistical computing environment.²⁵ Five participants had incomplete surveys at baseline such that prior CR scores could not be computed.

CR for these participants was estimated using single imputation with years of education and WTAR-FSIQ as linear predictors.

Conditional likelihoods were estimated using the lme4²⁶ and glmmTMB²⁷ packages for linear mixed-effects models. Time was modeled as a continuous variable ("Time") in years since baseline. Intervention group membership was encoded as a dummy variable ("group"). Data were in long-form, with a single column "Score" storing the z-scores for each test, and another column "test" denoting the cognitive test instrument ("test"), by-participant random coefficients were fitted for each instrument. Random slopes were not included in these models due to convergence issues. The formula for the adjusted model presented in Table S1 and Figure 1 is,

$$\text{glmmTMB} :: \text{glmmTMB}(\text{Score} \sim \text{PriorCR} + \text{scale}(\text{age}))$$

$$* \text{test} * \text{testTime} * \text{group} + (1 + \text{test} | \text{Participant})$$

The formula for the (adjusted) by-participant random intercept and slope models presented in Table 4 and Figure 2 is,

$$\text{lme4} :: \text{lmer}(\text{Score} \sim \text{scale}(\text{age}) + \text{PriorCR} * \text{Time} + \text{Time} * \text{group}$$

$$+ (1 + \text{Time} | \text{Participant}))$$

This model estimated by-participant slopes (which capture individual differences in practice effects) and population-level differences in these slopes between university study and comparison groups, adjusted for age and CR at baseline.

TABLE 3 Participant characteristics at each assessment (years since baseline)

	Years since baseline					
	0 (n = 485)	1 (n = 388)	2 (n = 393)	3 (n = 361)	5 (n = 308)	7 (n = 149 ^a)
Age (years)						
Mean (SD)	60.3 (6.8)	61.7 (6.8)	62.7 (6.6)	63.5 (6.7)	65.2 (6.6)	68.4 (6.5)
Age group						
50-59 years	233 (48.0%)	157 (40.5%)	135 (34.4%)	117 (32.4%)	77 (25.0%)	20 (13.4%)
60-69 years	205 (42.3%)	179 (46.1%)	195 (49.6%)	170 (47.1%)	144 (46.8%)	55 (36.9%)
70-79 years	47 (9.7%)	52 (13.4%)	61 (15.5%)	72 (19.9%)	81 (26.3%)	69 (46.3%)
80+ years	0 (0%)	0 (0%)	2 (0.5%)	2 (0.6%)	6 (1.9%)	5 (3.4%)
Gender						
Female	335 (69.1%)	262 (67.5%)	265 (67.4%)	243 (67.3%)	208 (67.5%)	108 (72.5%)
Male	150 (30.9%)	126 (32.5%)	128 (32.6%)	118 (32.7%)	100 (32.5%)	41 (27.5%)
Group						
Comparison	102 (21.0%)	82 (21.1%)	85 (21.6%)	76 (21.1%)	63 (20.5%)	40 (26.8%)
Intervention	383 (79.0%)	306 (78.9%)	308 (78.4%)	285 (78.9%)	245 (79.5%)	109 (73.2%)
Prior cognitive reserve (z)						
Mean (SD)	-0.003 (0.977)	0.019 (0.978)	0.055 (0.961)	0.017 (0.952)	-0.034 (0.949)	0.093 (0.826)

^aAssessments completed at time of analysis.

Note that the short-hand notation for an interaction of the form A * B * C expands to all main effects and lower-order interactions by convention in R, and the random effects structure is given in parentheses. The assumptions of linearity, homogeneity of variance, and normality of residuals were assessed using standard graphical methods, and were judged to be acceptable. Reproducible R code is provided at²⁸ and all estimated parameters are reported in Table 4 and the [Supplementary Tables](#).

To assess group differences in cognitive performance at entry into the study, Bayesian regression analysis was used to compare group means of cognitive tests scores, adjusted for age and CR (these covariates were also included in the primary analysis). Weakly informative student-t priors were specified, and Bayes factors were computed with bridge-sampling using the brms²⁹ package in R. Unlike p-values, Bayes factors allow a conclusion in favor of the null hypothesis (“no difference in cognitive test scores between groups at baseline”) to be drawn if supported by evidence. A concern is whether participants with lower test scores were more likely to drop out depending on whether they were in the university study group or comparison group. To test this we fitted a logistic regression model to estimate the expected probability of remaining in the study at year 5 conditional on the interaction between test scores (we used RAVLT scores) and intervention group.

3 | RESULTS

3.1 | Participants

Over 7 years (including up to six assessments per participant) of the project to 2019, this study included 2084 assessments and 37291 test scores (Table 3). At the time of data analysis, only 149 assessments

had been completed for the 7th year assessments, which are ongoing, and delayed due to coronavirus disease 2019 (COVID-19) restrictions. To the best of our knowledge, these restrictions did not discriminate against any part of our cohort, since they applied to all participants. The most commonly cited reason for withdrawing from the study was moving from Tasmania. Comparison group participants were significantly more likely to withdraw, with 112 leaving from the intervention group and 44 from the comparison group ($\chi^2 = 6.5, P = .01$); however, the proportion at each assessment varied little (Table 3). Nine participants were known to be deceased.

Participants in the intervention group completed a median (IQR) of 112.5% (50, 206) of 1-year full-time equivalent (FTE) study load (9 units). There were no discernable differences in groups on WTAR-FSIQ (mean IQ 112 for both groups), or early life education (median 12 years in both groups). At baseline, comparison group participants were older, with mean age of 63.2 years (SD 6.7 years) compared to mean age of 59.6 years (SD 6.6 years) for the intervention group, and had slightly lower prior CR z-scores (-.17 SD compared to .04 SD). Bayesian regression analysis (adjusted for age and prior CR) showed that there were no differences in mean cognitive test scores between groups at entry into the study ($\beta = .05, 95\%$ confidence interval (CI) .06, .16), $BF_{H_{alternative}/H_{null}} = .02$, which is strong evidence in favor of the null). Neither group was significantly more likely to remain in the study at year 5 depending on Rey Auditory Verbal Learning Test (RAVLT) scores at baseline ($P = .87$).

3.2 | Average of all cognitive tests

Aggregated over all cognitive test instruments, there was a significant time x group interaction after adjusting for age, prior CR, and a prior CR

TABLE 4 Unadjusted and adjusted (for age and prior CR) linear mixed-effects models assessing differences in trajectories of intervention group relative to the comparison group

Predictors	Score (z)			Score (z)		
	Estimates	95% CI	P	Estimates	95% CI	P
(Intercept)	-0.239	-0.338, -0.141	<.001	-0.199	-0.288, -0.109	<.001
Time (years)	0.013	0.002, 0.023	.016	0.044	0.032, 0.056	<.001
Group	0.170	0.059, 0.281	.003	0.035	-0.068, 0.138	.508
Time × group	0.021	0.009, 0.033	.001	0.020	0.008, 0.032	.001
Age (years)				-0.208	-0.251, -0.165	<.001
Prior CR (z)				0.143	0.100, 0.185	<.001
Prior CR × time				0.002	-0.004, 0.007	.499
Random effects						
σ^2	0.73			0.73		
τ_{00}	0.24 _{Participant}			0.19 _{Participant}		
τ_{11}	0.00 _{Participant-Time}			0.00 _{Participant-Time}		
ρ_{01}	0.53 _{Participant}			0.29 _{Participant}		
ICC	0.26			0.22		
N	485 _{Participant}			485 _{Participant}		
Observations	37291			37291		
Marginal R ² /conditional R ²	0.012/0.272			0.061/0.265		

× time interaction ($P = .001$). Participants in the intervention group had a $z = .02$ SD [95% CI .01, -.03] per year increase in standardized scores relative to comparison group (Table 4). These estimates were identical to three significant digits in an unadjusted analysis (Table 4). After accounting for the group-level (fixed) effects of time and the group × time interaction, and by-participant (random) intercepts, there was little individual variation in slopes.

3.3 | Group differences on specific cognitive tests

There was a significant time × group × test interaction ($P = .016$), suggesting that relative to the comparison group, intervention group trajectories differed across tests. Analysis of deviance statistics for the adjusted and unadjusted models, and a detailed table of coefficients and their CIs are reported in Table S1. Post hoc analysis using estimated marginal mean trends showed that the significantly different group trajectories were for Boston Naming Test (BNT) ($z_{\text{control-intervention}} = -.043$ SD [standard error (SE) .017], $P = .009$), RAVLT recall ($z_{\text{control-intervention}} = -.041$ SD [SE .016], $P = .012$), RAVLT total ($z_{\text{control-intervention}} = -.056$ SD [SE .016], $P < .001$), Wechsler Adult Intelligence Scale (WAIS) comprehension ($z_{\text{control-intervention}} = -.038$ SD [SE .016], $P = .022$), and spatial span (SSP) length ($z_{\text{control-intervention}} = .040$ SD [SE .017], $P = .017$). All differences favored the intervention group, with the exception of SSP length. Broadly, the greatest differences were observed on those tests that displayed the weakest practice effects over repeated tests (illustrated in Figure 1, and Table S2, which shows the estimated marginal mean time-trends and post hoc contrasts).

3.4 | Age

Participant age had a significant effect on cognitive trajectories ($P < .001$), with a 1 SD (≈ 7 year) increase in age-reducing standardized cognitive test slopes by $z = -.027$ SD [95% CI -.037, -.017]. The estimated annualized difference between intervention and comparison group participants was $z = .009$ SD [-.002, -.02] per year of participant age, but this was not statistically significant ($P = .122$; Figure 2, Table S3).

3.5 | Academic load

Aggregated over all test instruments, the dose-dependent effect of academic load was estimated to be $z = .004$ SD [95% CI -.0004, .0094] per year, but this was not a statistically significant interaction ($P = .07$). Cognitive trajectories on different test instruments did not vary significantly with academic load. There was a significant main effect of prior CR ($z = .121$ SD [.033, -.209], $P < .001$), but the effect of CR on cognitive trajectories was not statistically significant ($z = .004$ SD [-.006, .013], $P = .125$) and did not appear to benefit comparison or intervention groups differentially ($z = .001$ SD [-.010, .013], $P = .821$).

4 | DISCUSSION

The current study shows that later-life university study improved cognitive trajectories when compared with participants who did not undertake university study. The benefits of university study were

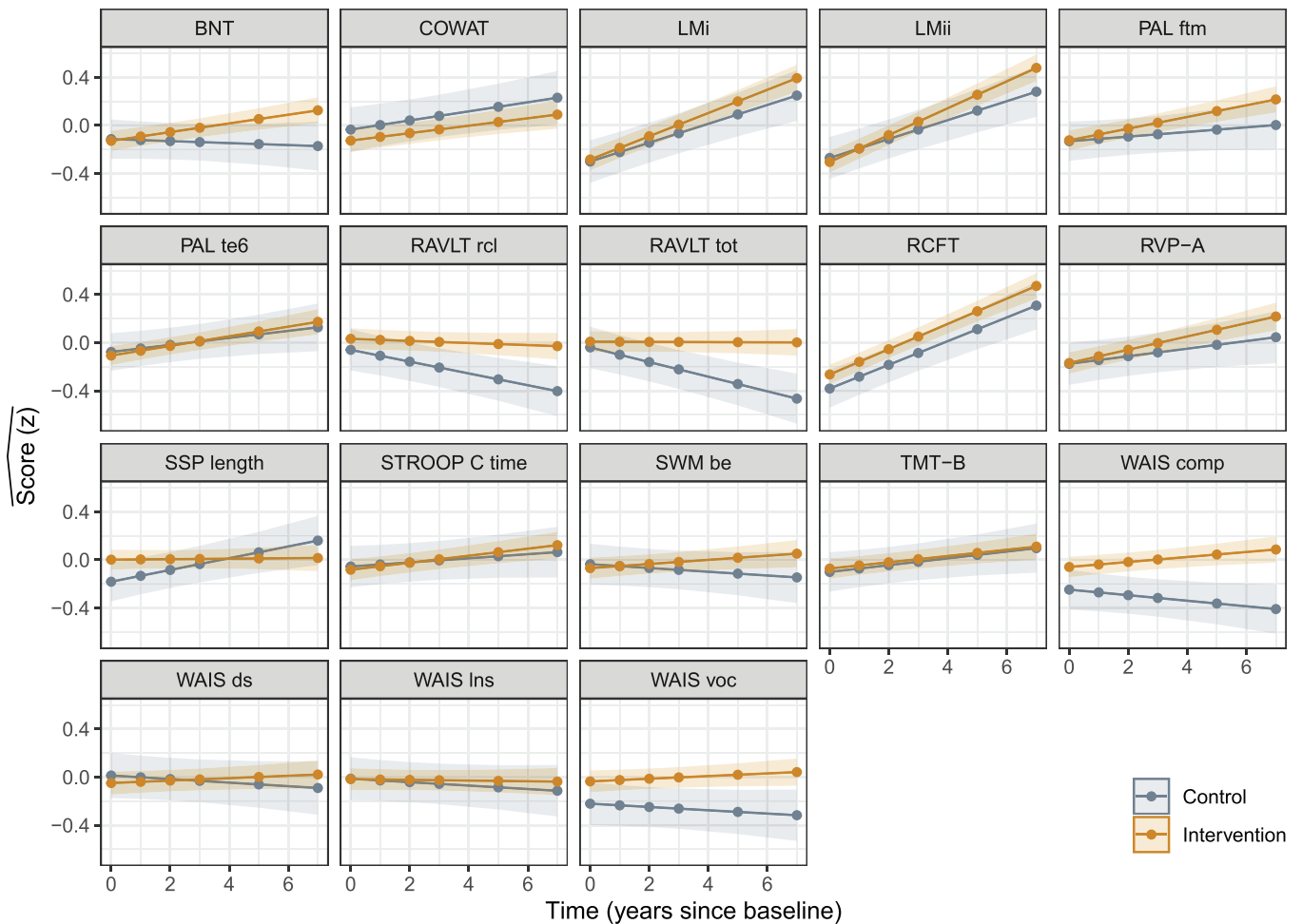


FIGURE 1 Estimated cognitive trajectories (with 95% confidence intervals [CIs]) over years since baseline for intervention group participants (those who undertook university study) and the comparison group (those who did not), holding age at entry into study and cognitive reserve (CR) at their respective means. The greatest group differences appear in tests where comparison group participants did not appear to benefit from re-test practice effects: tests of verbal memory, vocabulary, and comprehension

greatest in tests on the domains of verbal memory, verbal episodic memory, and language processing. These tests also had the weakest practice effects (evidenced by estimated marginal time-trends for the comparison group). Older participants benefited the least from practice effects and the most from the intervention, particularly on verbal learning, memory, naming, and comprehension tests. Notably, tests that relate to executive function and visuo-structural memory showed no benefit relative to university study.

This was a purposeful longitudinal study by design, focused on a real-world intervention and formal tertiary-level education, and follows a substantial number of studies indicating low levels of educational attainment early in life as a known risk-factor for dementia.³⁰ With comprehensive neuropsychological data at the mid-point of the study, the current results indicate that engagement in education by older adults provides a protective benefit for specific areas of cognitive function.

Previous assessments of cognitive trajectories in the THBP have used factor-derived composite scores of cognitive function.^{16,17} For this analysis, we chose to report standardized scores on test instru-

ments used in the THBP assessment battery. Shared and un-shared test variance was partitioned through the model structure to estimate conditional likelihoods for each group and the characteristic trajectories of each test, giving a detailed and directly comparable picture of expected cognitive trajectories on often-used cognitive tests. Substantial variation in trajectories on cognitive test instruments was demonstrated, along with variation in the estimated difference between intervention and comparison groups on these trajectories. There is established evidence that age-related cognitive change is not universal across all cognitive domains.¹ The domains on which the intervention group performed most strongly—verbal fluency and episodic memory—are domains that have been found previously to be most vulnerable to age-related decline.¹⁵ For tests on other domains, there was little difference in trajectories between intervention and comparison groups, with both groups appearing to benefit from familiarity with the tests. These re-test practice effects did not appear to be moderated by prior CR, which appeared to benefit only the *level* of age-adjusted cognitive test performance, rather than the *slope* (similar to other findings for early life education as a proxy of CR; see²³ and²² for reviews). A plausible

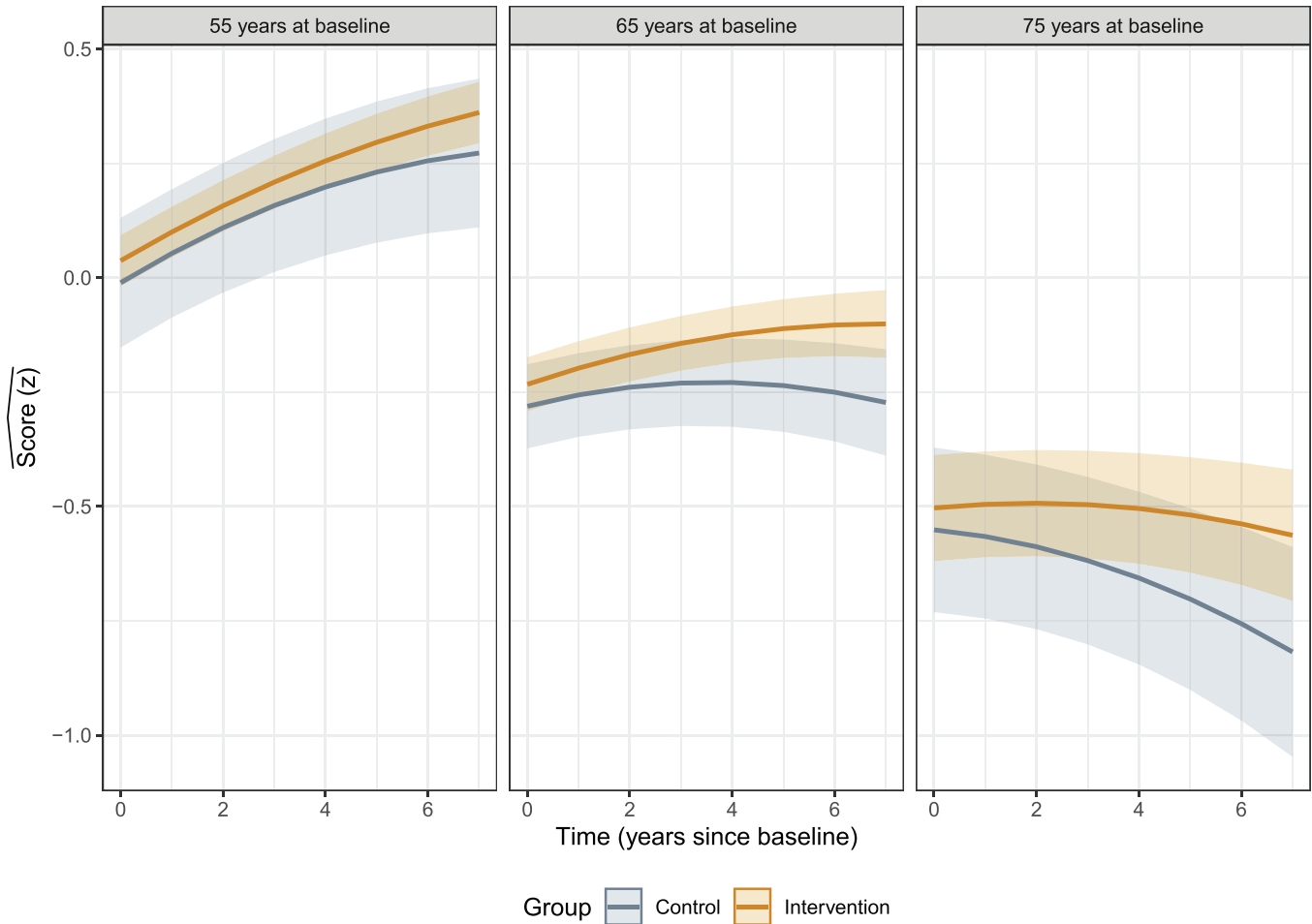


FIGURE 2 Estimated mean cognitive trajectories (with 95% confidence intervals [CIs]) over the years since baseline for intervention group participants (those who undertook university study) and the comparison group (those who did not), holding prior cognitive reserve (CR) as the mean value. Panels show expected trajectories for participants at 55, 65, and 75 years of age at entry into the study. Re-test practice effects are most evident in the panel showing expected trajectories for someone entering the study at age 55. Older participants benefited from re-test practice effects the least and appeared to gain the most from later-life university education. The model decomposes age and re-test time (in years since first assessment) as separate effects, so estimated trajectories are quadratic

interpretation is that later-life education has a preservation or compensatory effect, rather than augmenting that which was not lost. Further work could explore potential differences between early and later-life education in building CR, and how that relates to biological processes of development and aging.

The cognitive tests in the battery were not designed to be administered repeatedly over time, although, to minimize practice effects, some of these instruments included alternative forms. Although we anticipated that the relatively long inter-trial intervals (12 and 24 months) would minimize practice effects, it is apparent that some tests (eg., logical memory, Rey complex figure) had substantial practice effects. These were also the tests where the least apparent benefit of later-life education was observed. For statistical adjustment, we assumed that these practice trajectories were linear, but power-law or non-linear location-scale models³¹ might be more appropriate as participants start to hit the practice effect ceiling.

Adults in mid-life and post-retirement form a growing cohort who are engaging in university-level education³² around the world. This

has included retirement complexes established on college/university grounds, with the capacity for older adults to engage in education on an audit basis. With respect to the current study results, it is unknown what dimension of university study is important (eg, lectures, tutorial or practical sessions, assessments, social interaction), or whether the sum of these experiences provides the benefit. Structured multi-modal interventions have been the focus of many randomized-controlled trials (FINGER and Disability and Multidomain Alzheimer Preventive Trial), resulting in no³³ or small effect size¹⁴ improvements in cognitive function, with none yet showing mitigation of cognitive decline. These studies have been limited in duration, with subjects the relatively passive recipients of intervention. The key limitation of the current study is the lack of randomization to "treatment." This was a pragmatic design, balancing practical and ethical considerations against internal validity and generalizability. This raises questions about whether participants who opted into the intervention arm of the trial had greater capacity to undertake or benefit from later-life education. Although our groups did not differ at baseline on mean cognitive test

scores, or on other measures such as anxiety, depression, and CR,¹⁶ this does not rule out the existence of other unmeasured resources and capacities that differed between groups. For example, there is a growing body of evidence that perceived control and self-efficacy are associated with cognitive test performance.³⁴ It is plausible that participants with higher baseline self-efficacy who chose to participate in university education and differences in cognitive test performance over time were correlated with this unmeasured selection bias.

The study is limited to an individual island community, with most Tasmanians being of predominantly European ancestry. Generalizability of findings to other populations would require further study. Conversely, this also likely supports the case-control feature of the study, as both comparison and intervention groups would have more uniform life experiences. As a turn-key intervention that is amenable to inclusion in public health measures relevant to aging-related cognitive decline, accessibility is an important factor. Participants in the THBP had subsidized course fees, and Australian course fees are relatively low for domestic students. University course fees vary substantially around the world, to being mostly free or low-cost in many European countries to costly in high-prestige US tertiary institutions. Although university study also usually requires access to additional resources, such as location close to a provider and computer/internet access, the COVID-19 pandemic has also meant that most university providers have developed comprehensive online offerings, which may improve access to a broader range of potential participants.

We have previously demonstrated that age alone had no impact on academic achievement (grade point average) in this cohort.³⁵ Despite flatter cognitive trajectories overall, older participants appeared to obtain relatively more benefit from later-life university study than younger participants. Although these estimates were not statistically significant, they suggest that increasing age does not necessarily diminish the benefits conferred from later-life education.

There has been no qualitative analysis of participant experiences in the THBP; however, anecdotal reports from participants suggest that many have enjoyed being able to study without career expectations or the pressures that normally accompany higher education. The freedom to choose an area of study may be an important factor, both for subjective well-being, and to encourage ongoing compliance and motivation to engage with the intervention over a duration of years. In addition, social aspects of the on-campus study experience may contribute to subjective well-being and cognitive health, albeit we have previously shown no differences in social networks between intervention and comparison groups.¹⁶ Collectively, the current study supports the value of a complex, real-world intervention in the form of engagement in university study to attenuate decline in specific cognitive domains. The long-term goal of the THBP over 15 years is to collect extended longitudinal data from a single cohort to examine whether additional education later in life is associated also with reduced risk of dementia. The long-term nature of the THBP, as well as the relatively high retention rate of subjects, will determine if there is a subsequent mitigation of risk for significant cognitive decline and dementia.

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AUTHOR CONTRIBUTIONS

Aidan D. Bindoff conducted statistical analysis, wrote the first draft, and finalized the final draft. Mathew J. Summers designed the study, recruited participants, conducted neuropsychological assessments, and contributed to interpretation. Edward Hill contributed to data collection and literature review. Jane Alty contributed to interpretation. James C. Vickers designed the study, recruited participants, and contributed to interpretation. All authors contributed to the writing and review of the article.

CONFLICTS OF INTEREST

Mathew J. Summers and James C. Vickers were awarded National Health and Medical Research Council (NHMRC) grant funding to their institutions for the current work. Aidan D. Bindoff, Mathew J. Summers, Edward Hill, Jane Alty, and James C. Vickers were awarded NHMRC grant funding to their institutions outside of the current work. Mathew J. Summers was awarded European Commission Horizon 2020 grant funding to his institution outside of the current work. James C. Vickers was awarded Medical Research Futures Fund, FightMND, and Royal Hobart Hospital Research Foundation grant funding to his institution outside of the current work. James C. Vickers has also served as an unpaid board member to Glenview Community Services and the Dementia Australia Research Foundation. Jane Alty was paid royalties for medical textbooks, and honoraria, accommodation and speaking fees paid to herself within the last 36 months, unrelated to the current work.

DATA AVAILABILITY STATEMENT

De-identified data analyses and study protocols may be shared by contacting the corresponding author. Reproducible statistical analysis code examples are available at https://github.com/ABindoff/thbp_7years.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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