Reevaluating the role of education on cognitive decline and brain aging in longitudinal cohorts across 33 Western countries

Nature Medicine

July 2025

Section: Pg. 1-10; ISSN: 1078-8956,1546-170X

Length: 11057 words

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Body

Abstract

Why ***education*** is linked to higher ***cognitive*** function in ***aging*** is fiercely debated. Leading theories propose that ***education*** reduces ***brain*** ***decline*** in ***aging*** and enhances tolerance to ***brain*** pathology or that it does not affect ***cognitive*** ***decline*** but, rather, reflects higher early-life ***cognitive*** function. To test these theories, we analyzed 407,356 episodic memory scores from 170,795 participants older than 50 years, alongside 15,157 ***brain*** magnetic resonance imaging scans from 6,472 participants ***across*** ***33*** ***Western*** ***countries***. More ***education*** was associated with better memory, larger intracranial volume and slightly larger volume of memory-sensitive ***brain*** regions. However, ***education*** did not protect against ***age***-related ***decline*** or weakened effects of ***brain*** ***decline*** on cognition. The most parsimonious explanation for the results is that the associations reflect factors present early in life, including propensity of individuals with certain traits to pursue more ***education***. Although ***education*** has numerous benefits, the notion that it provides protection against ***cognitive*** or ***brain*** ***decline*** is not supported.

In a large cross-national study, ***education*** was linked to better memory and larger ***brain*** volumes but not to slower ***cognitive*** or ***brain*** ***decline*** with ***age***, suggesting that the association reflects early-life factors rather than neuroprotective effects in ***aging***.

Main

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Although the total number of people with dementia will increase substantially due to population growth and aging1, the incidence seems to be declining2,3, and older adults have better ***cognitive*** function today than 20 years ago4. One hypothesis is that this reflects broad societal and individual lifestyle changes and that dementia incidence can be further reduced by promoting these1,5. ***Education*** has repeatedly been suggested to be one such potential protective factor6,7, in line with observations of robust associations between ***education*** and higher ***cognitive*** function in ***aging*** as well as ***declines*** in dementia incidence with increasing population ***educational*** attainment8,9. However, results thus far are heterogeneous and point in different directions, and the specific mechanisms that could explain such a causal link are widely debated10. We, therefore, suggest addressing these questions by conducting a large mega-analysis of ***longitudinal*** ***brain*** and ***cognitive*** studies covering a wider geographical distribution of samples.

Education could result in better cognition in ***aging*** by contributing to a lower rate of ***age***-normative ***brain*** decline11—that is, '***brain*** maintenance'—which has been associated with better episodic memory12. Studies have reported that older adults with higher ***education*** have less ***brain*** pathology13, less ***brain*** ***decline*** in presymptomatic dementia14 and less accumulation of cerebrovascular lesions15. However, a recent ***longitudinal*** study investigating two independent samples did not find different rates of change in hippocampus and ***age***-sensitive regions of the cerebral cortex in more ***educated*** participants16. Alternatively, ***education*** could make people more resilient to underlying ***brain*** pathology—that is, yielding higher '***cognitive*** reserve'17. According to this theory, ***education*** leads to more efficient processing of ***cognitive*** tasks, which, in turn, allows for higher performance despite ***age***-normative levels of ***brain*** decline18. Although a popular theory5,19, a ***longitudinal*** study found that ***education*** did not weaken the link between hippocampal atrophy and memory change20. Both the maintenance and the reserve accounts of ***education*** imply that ***education*** causally influences late-life cognition by reducing or postponing ***age***-related ***decline***. This is controversial, however, because even though ***education*** is associated with better ***cognitive*** function among older adults, it is not clear that more ***educated*** persons show less ***cognitive*** ***decline*** when measured longitudinally21,22.

An alternative perspective holds that the association between ***education*** and ***cognitive*** performance is persistent ***across*** the adult lifespan. This contrasts with the more ***aging***-centered views presented above. Under this alternative view, if ***education*** has a positive causal effect on cognition in ***aging***, it would be by permanently boosting ***cognitive*** function earlier in life, causing persistent differences between ***educational*** groups. Increased compulsory schooling has been shown to elevate scores on tests of memory23, 24–25, intelligence26,27 and general cognition28, with effects detectable decades later29. This perspective could also be consistent with a lack of causal effects of ***education*** on ***cognitive*** function, however, as those with higher initial ***cognitive*** functioning would be expected to reach higher levels of ***education*** than their peers. Hence, the topic of the ***role*** of ***education*** in ***cognitive*** function and ***brain*** health in ***aging*** is riddled with controversies30.

Nonetheless, contrasting predictions can be derived from the different theories. If ***education*** improves memory in older ***age*** by shaping ***brain aging***, we expect better preservation of memory-sensitive ***brain*** regions among individuals with higher ***education***. If ***education*** improves ***cognitive*** reserve, we expect more tolerance to ***brain*** pathology, indexed by a lower correlation between ***brain*** ***decline*** and ***cognitive*** ***decline***. In contrast, if the ***education***–memory–***brain*** relationship reflects stable individual differences, ***education*** should not correlate with either memory or ***brain*** ***decline***. In that case, we also would expect to see selection effects, in the sense that participants with specific traits, especially higher ***cognitive*** function, are more likely to pursue further ***education***. It is also relevant to examine whether re-test effect—the tendency for performance to increase as a function of previous tests taken—is exaggerated with higher ***education***. If more ***education*** yields ***cognitive*** reserve, this may manifest as a greater ability to take advantage of previous testing experience and to develop more efficient test-taking strategies.

A major challenge in addressing these questions is that large, representative and heterogeneous ***longitudinal*** samples with sufficient statistical power are needed. The geographic coverage is critical, because relationships may vary ***across*** time31 and societies32,33. For example, the population attributable fraction (PAF) of dementia due to low ***education*** varied from 1.7% in Argentina to 10.8% in Bolivia in a study of seven Latin American countries34. We compiled data from ***33*** ***countries*** ***across*** Europe, the United States and Israel, including a total of 407,356

memory tests from 170,795 participants with up to seven follow-up sessions (Fig. 1a), ensuring that the results are not confined to one specific time and place. Still, because the samples come from ***Western***, ***Educated***, Industrialized, Rich, Democratic (WEIRD) ***countries***, we compare the results to patterns from non-WEIRD societies in Africa, Latin America and East and South Asia35.Fig. 1

Geographical and *age* distribution of samples.

a, Total number of completed memory test sessions per ***country***. **b**, Number of ***brain*** MRI scans per ***country***. Maps were generated using the IMAGE Interactive map generator (*https://gisco-services.ec.europa.eu/image/*).

Episodic memory is a unique memory system36 that can be defined as the ability to recall information tied to a specific time or place, in contrast to semantic memory, which is recall of general knowledge and facts37. In research and clinical assessments of memory function, episodic memory is typically measured as the amount of newly acquired information that can later be explicitly recalled, such as the number of words remembered from a presented list. We focus on episodic memory because it is a particularly ***age***-sensitive long-term memory system38, and we assess it using a verbal recall test, one of the most employed methods.

To address ***brain*** mechanisms, we analyzed 15,157 ***brain*** magnetic resonance imaging (MRI) scans and concurrent memory tests from 6,472 participants ***across*** seven ***countries*** (Fig. 1b). ***Brain decline*** was defined as within-participant reductions over time in memory-sensitive ***brain*** regions. The primary data sources were the population-based multinational Survey of Health, Ageing and Retirement in Europe (SHARE) (*https://share-eric.eu/)39* and the Lifebrain consortium40 (*https://www.lifebrain.uio.no/*), enriched with legacy databases. For sample representativity, SHARE uses the best available sample frame resources in each ***country*** to achieve full probability sampling, including access to population registers. The MRI populations vary in representativity, and, hence, we validate the memory results from SHARE in the MRI samples before conducting the ***brain*** analyses.

Results

SHARE *cohort* results

Episodic memory was assessed with a 10-word verbal recall test, with two conditions (immediate and 5-minute recall), using multiple versions ***across*** waves and participants41. Each condition was separately included in the statistical models, yielding two observations per timepoint per participant. Generalized linear models (GLMs) with a binomial link were run using memory score as dependent variable, with the interaction between ***education*** and time since baseline as the critical term, using test type (immediate or 5-minute delay), a monotonic function of the number of previous tests taken (to control for re-test effects), ***education***, self-reported sex, ***country***, baseline ***age*** (smooth function), time since baseline and the ***age*** × time interaction as covariates. Individual-specific intercepts per participant were nested within ***country***. *z*-transformed values for ***age*** and time were used in the model fitting and converted back to natural units when showing the results. Memory offset refers to the cross-sectional differences between groups—that is, main effect of ***education***. Memory change was defined as change in memory over time within participants, with differences between ***education*** groups represented by the ***education*** × time interaction. The main outputs of the statistical model were the odds ratios of remembering a word compared to a reference group. For readability, we used simplified terms for ***education*** categories, with definitions, SHARE categorization and mapping to the International Standard Classification of ***Education*** (ISCED) presented in Supplementary Information.

Memory scores were lower with higher baseline ***age***, showing slightly accelerating trajectories (smoothing parameter for the combined sample = 45.8, confidence interval: 20.7–81.5). Figure 2a revealed a perfect ordering of higher scores with more ***education*** ***across*** ***age***. 'No ***education***' had an odds ratio of 0.54 (Cohen's $d = -0.33$) compared to the reference category ('High school'), whereas 'Master's' had an odds ratio of 1.55 (Cohen's $d = 0.24$) (Fig. 3a and Extended Data Table 1), yielding an odds ratio range of 1.01 and a Cohen's d range of 0.57. This confirms the well-known positive association between ***education*** and episodic memory in ***aging*** and shows that the difference in memory score is almost identical with each increase in ***education*** category.Fig. 2

***Age*, *education* and practice effects on memory.**

a, Memory score trajectory over ***age***. The *y* axis denotes memory score on the logit scale, and the lines show the predicted memory performance over baseline ***age*** for each ***education*** category. **b**, Re-test effects for each ***education*** group. **c**, Comparing re-test effects for each ***education*** group to the 'High school' group, lines show the ratio of odds ratio for the given ***education***/odds ratio for 'High school' (dashed horizontal line). Shaded areas denote 95% confidence interval.

Fig. 3

Associations among *education*, memory score and memory score *decline*.

a, Associations between ***education*** and memory offset scores expressed by odds ratios. **b**, Associations between ***education*** and ***decline*** in memory scores expressed by odds ratios. 'High school' is used as reference (dashed line). Error bars denote 95% confidence interval and odds ratio. Results are based on 130,880 unique participants and 352,953 memory tests. ref., reference.

Re-test effects were substantial and, thus, essential to adjust for in analyses of change. Odds ratios increased almost linearly, from 1.5 compared to baseline at the first follow-up to 2.5 at the fifth follow-up (Fig. 2b). A small negative effect of time (1 year) was observed on memory scores (odds ratio = 0.963, confidence interval: 0.961–0.964), slightly increasing with ***age*** (***age*** × time odds ratio = 0.9981, confidence interval: 0.9980–0.9982). These results show that test scores increase when participants are tested repeatedly but that scores become lower over time when this is accounted for. Testing whether higher ***education*** was associated with less memory ***decline*** (Fig. 3b and Extended Data Table 2), we found negligible effect sizes—all odds ratios less than 1.005—meaning that there were no meaningful differences. Furthermore, no systematic differences were observed in re-test effects between participants of different ***education*** levels (Fig. 2c). Although the immediate and delayed recall conditions were highly correlated ($r = 0.74$), the delayed condition was more difficult and likely to a larger extent reflected long-term memory. We repeated the analyses for each condition separately, yielding identical results (Supplementary Figs. 5 and 6).

The first set of analyses showed that ***education*** was linearly associated with better memory scores but not differences in memory ***decline*** or re-test effects. To test the hypothesis that the ***education***–memory associations reflect selection effects, we re-ran the analyses using 'relative' ***education*** as measure of interest. That is, for each participant, we calculated amount of ***education*** relative to the other participants from the same birth ***cohort***, sex and ***country***. This yielded a percentile score for each participant (0–100%), indexing amount of ***education*** relative to similar peers. This analysis provides a test of selection effects on ***education***–memory associations—that is, that people with some unmeasured traits take more ***education***—and this trait is correlated with late-life memory scores. Absolute level of ***education*** was used as covariate, as absolute and relative ***education*** would be correlated. By using relative ***education***, we were able to partially account for these selection effects that vary between men and women from different birth ***cohorts*** in ***countries*** with widely varying ***educational*** opportunities and experiences. Birth ***cohort*** was measured in bins of a decade (1900–1909, 1910–1919, …, 1960–1969). The results showed that including relative ***education*** in the model reduced the associations between absolute ***education*** and memory, whereas relative ***education*** showed an independent, positive association with memory. The effects were modest, as moving from the lowest (0) to the highest (100) percentile was associated with an odds ratio of 1.17 (confidence interval: 1.14–1.20)/Cohen's $d = 0.08$ compared to the reference group ('High school') (Supplementary Fig. 10). This suggests that selection effects explain some of the association between ***education*** and memory in ***aging***.

Further support for selection effects would be if variables reflecting individual differences in childhood, before or in the first years of schooling, could account for the associations later in life. We re-ran the analyses controlling for two proxies of earlier-life ***cognitive*** function—self-assessed mathematical and language skills at ***age*** 10 years—as well as a proxy of 'parents' scholarly culture'42— number of books in the house at ***age*** 10 years. If this reduced the association between episodic memory scores and ***education***, this would support the hypothesis of selection effects. The three childhood variables were all significant confounders of the association between ***education*** and

memory score (math: estimate = 0.104, confidence interval: 0.099–0.108; language: estimate = 0.118, confidence interval: 0.114–0.123; books: estimate = 0.083, confidence interval: 0.079–0.087). When controlling for them, the association was reduced: the odds ratio and Cohen's *d* ranges from the original model were 1.01 (0.54–1.55) and 0.58 (−0.34 to 0.24), respectively, whereas the adjusted model ranges were odds ratio 0.60 (0.65–1.25) and Cohen's *d* 0.36 (−0.24 to 0.12). This shows that a part of the late-life association between ***education*** and memory score could be explained by self-reported childhood ***cognitive*** function and home environment. For the analyses of intra-individual memory ***decline*** over time, controlling for each childhood variable further reduced the already minute associations with memory recall, rendering none of them statistically significant (full results in Supplementary Information).

Sensitivity analyses SHARE

To explore whether the results were specific to the verbal recall test, we first repeated the analyses for two additional tests from SHARE (Supplementary Information). 'Numeric skill' yields a measure of mathematical ability, and 'orientation for time and place' is a test sensitive to ***age***-related ***cognitive*** ***decline***. Similar to the verbal recall results, scores were perfectly ordered according to ***educational*** level for both tests (Fig. 4a–d), with effect sizes numerically slightly larger (orienting: odds ratio range = 1.0 (0.26–1.26), Cohen's *d* range = 0.86 (−0.74 to 0.12); numeracy: odds ratio range = 1.48 (0.31–1.79), Cohen's *d* range = 0.96 (−0.64 to 0.32)). ***Age*** slopes were parallel, with minute ***education***–change associations: odds ratio range 0.982–1.007 for orientation and 0.982–1.002 for numeracy. Hence, the pattern of results for verbal recall generalizes to two other tests.Fig. 4

Sensitivity analyses.

a, Numeracy score trajectory over ***age***. The *y* axis denotes numeracy score on the logit scale, and the lines show the predicted numeracy performance over baseline ***age*** for each ***education*** category. **b**, Orientation score trajectory over ***age***. The *y* axis denotes orientation score on the logit scale, and the lines show the predicted orientation performance over baseline ***age*** for each ***education*** category. Shaded areas represent 95% confidence intervals. **c**, Offset results: Cohen's *d* for each ***education*** category compared to the reference category ('High school') for three ***cognitive*** tests from SHARE. **d**, ***Longitudinal*** change results. **e**, Cohen's *d* compared to the 'High school' category in SHARE-HCAP. **f**, Effects for memory (HCAP) compared to the 'Middle school' category ***across*** culturally diverse samples.

To explore whether the results could be replicated with a more comprehensive test battery, we analyzed the recently released comprehensive ***cognitive*** test protocol administered to a subsample of participants at the latest wave of the survey (SHARE-HCAP (Harmonized ***Cognitive*** Assessment Protocol); Supplementary Information). We screened out ***cognitive*** impairment and restricted the sample to participants older than 65 years, yielding 25 test scores from 1,380 participants, including 11 memory scores. Due to the smaller sample, four ***education*** categories were used (primary or less $n = 115$, middle school $n = 192$, high school $n = 608$, vocational or university level $n = 465$). We used principal component analysis (PCA) to extract individual-level scores for four ***cognitive*** domains (episodic memory, executive function, language and verbal fluency and orientation). Associations between ***education*** and performance were monotonously positive for all domains (orientation Cohen's *d* range (minimum, maximum) = 0.74 (−0.29 to 0.45); episodic memory range = 1.22 (−0.54 to 0.68); executive range = 1.03 (−0.24 to 0.79); language range = 1.00 (−0.36 to 0.64) (Fig. 4e)). The ***age*** trajectories were close to parallel (Supplementary Information), except for more complex curves for the lowest ***education*** level, probably due to few participants in this group. This demonstrates that the main results for verbal recall are generalizable to other ***cognitive*** tests and domains.

The data cover ***33*** ***countries*** in different continents but are restricted to WEIRD societies. To explore whether the results generalized to non-WEIRD societies, we plotted the memory component score from SHARE-HCAP against memory scores from a recent HCAP study of 16,524 older participants (59–78 years) in three non-WEIRD ***countries*** (China, India and South Africa) and one partially WEIRD ***country*** (Mexico)35. In these studies, substantial efforts were devoted to validating HCAP ***across*** widely different cultures. Although ***education*** and mean scores differed greatly compared to SHARE42, with less than 10% of participants from South Africa and

China having high school ***education*** or more, associations were remarkably similar (Fig. 4f). In all non-WEIRD samples, there were monotonous, almost linear relationships between ***education*** and higher memory scores, mimicking the SHARE-HCAP results. This suggests that the present cross-sectional ***education***–memory associations are not restricted to WEIRD societies only.

Brain MRI ***cohort*** results

Thirteen datasets with ***longitudinal*** MRI, memory assessments and information about ***education*** were included from seven ***countries*** ***across*** the North to South of Europe, the United States and Canada (Fig. 1b). In addition to ***cohort***-specific inclusion and exclusion criteria, all participants were older than 50 years without ***cognitive*** impairment or neurological or psychiatric disorders. The initial dataset included participants with 1–14 MRI acquisitions with follow-up intervals up to 15.8 years and 1–24 memory assessments with follow-up intervals up to 28 years. Sample characteristics are presented in Extended Data Table 2, and ***cohort***-specific descriptions are presented in Methods.

First, we tested whether the main ***cognitive*** results from SHARE replicated in the MRI ***cohorts***. As ***education*** coding varied, we could not use the SHARE coding scheme, and ***education*** was, hence, dichotomized based on the median split for each sample, with post hoc analyses using 'Higher ***education***' (***education*** after high school) versus 'Secondary ***education***' (high school or lower) ('replication analyses'). A generalized additive mixed model (GAMM)43 was run using memory (z-normalized based on the first observation per each dataset) as dependent variable, with ***education***, time since baseline, sex and a dummy for re-test effects as fixed effects and baseline ***age*** as smooth term. Random intercepts were included per participant and dataset, and random slopes of re-test and time were included for each dataset. To test memory change, an ***education*** × time interaction term was added to the model.

Similar to the SHARE results, whereas high ***education*** was associated with better memory scores ($\beta = 0.33$, s.e. = 0.009, $P < 0.001$, Cohen's $d = 0.63$), the ***education*** groups showed close to parallel changes over time (Fig. 5d,e). Predicted change over 10 years was $z = -0.20$ for high ***education*** compared to $z = -0.26$ for low ***education*** (effect of ***education*** group on memory z-score change per year: $\beta = 0.006$, s.e. = 0.003, $P = 0.029$, Cohen's $d = 0.01$) (for complete results, see Supplementary Information). Similar results were seen when using the alternative ***education*** categorization. This confirmed that the main findings from SHARE were also seen for the memory tests in the ***brain*** MRI ***cohorts***.Fig. 5

Education, ***brain*** measures and episodic memory.

a, ***Brain*** regions where changes in structure and memory were related (FDR < 0.05) are highlighted, with color intensity reflecting the strength of each region's loading on the PC. The nucleus accumbens and left inferior lateral ventricle are not shown. **b**, Predicted ***brain*** PC score over baseline ***age***. **c**, Three-year ***brain*** change (PC) for the high (green) and low (orange) ***education*** categories. The lines represent the predicted ***brain*** PC score as a function of time in each category. Shaded areas represent the s.e. of subject-level predictions. **d**, Predicted memory score over baseline ***age*** in the MRI ***cohorts***. **e**, Three-year memory change for each ***education*** category. The lines represent the predicted memory score as a function of time in each category. Shaded areas represent 95% confidence intervals.

Next, we extracted a ***brain*** variable sensitive to memory change. For each participant, annual change in each of 166 ***brain*** regions was calculated and related to memory change by a series of linear mixed-effect models, yielding 29 false discovery rate (FDR)-corrected significant regions (Fig. 5a). These were entered into a PCA, yielding a memory-sensitive ***brain*** principal component (PC). This PC could then be used to test the specific hypothesis that high ***education*** has protective effects on ***brain*** change relevant for episodic memory and the prediction from the ***cognitive*** reserve theory that highly ***educated*** participants would experience less memory ***decline*** for a given level of ***brain*** ***decline***.

To test the association between ***education*** and ***brain*** PC score (offset effects), a GAMM was run with ***education***, time since baseline, sex and estimated total intracranial volume (eTIV) as fixed effects and baseline ***age*** and sex ×

baseline ***age*** as smooth terms. Random intercepts were included per participant, scanner and dataset, and random slopes of time were included for each dataset. The ***brain*** PC showed the expected negative relationship to ***age***, slightly accelerating from about 70 years (Fig. 5b), and time ($\beta = -0.07$, s.e. = 0.008, $P < 0.001$). Estimated loss in the high ***education*** group was $z = -0.68$ over a decade compared to $z = -0.74$ for the low group (interaction effect of ***education*** × time on ***brain*** volume: $\beta = 0.005$, s.e. = 0.002, $P = 0.015$, Cohen's $d = 0.024$), yielding close to parallel change slopes (Fig. 5c). Hence, ***brain decline across*** memory-sensitive ***brain*** regions was very similar in the two ***education*** groups.

In contrast, high ***education*** was slightly positively associated with the ***brain*** PC ($\beta = 0.04$, s.e. = 0.02, $P = 0.049$, Cohen's $d = 0.17$) and intracranial volume ($\beta = 0.12$, s.e. = 0.002, $P < 0.001$) (Fig. 6a). This means that participants with high ***education*** on average had slightly larger regional ***brain*** volumes, smaller ventricles and larger head size. The association with intracranial volume was numerically larger than the association with the ***brain*** PC. Intracranial volume is developed in childhood and undergoes minimal changes during school ***age***, suggesting that this association reflects selection effects.Fig. 6

Relationships among *brain*, memory and *education*.

a, eTIV in the high ($n = 3{,}800$) versus low ($n = 2{,}672$) ***education*** category. The center of the box is the median eTIV for each group, and the whiskers extend to ±1.5 s.d. × interquartile range. **b**, Predicted memory score as a function of baseline ***brain*** PC ***across education*** categories. **c**, Predicted memory score over time as a function of ***brain*** PC score for each ***education*** category. Shaded areas represent s.e. of subject-level predictions.

Finally, we tested whether the prediction from the ***cognitive*** reserve theory that the relationship between ***brain decline*** and memory ***decline*** is weaker in participants with higher ***education***. First, a positive relationship was observed between the ***brain*** PC and episodic memory score ($\beta = 0.073$, s.e. = 0.013, $P < 0.001$). Because the ***brain*** PC was extracted from regions where ***brain*** change was related to memory change, the memory change–***brain*** change relationship was given ($\beta = 0.01$, s.e. = 0.002). More importantly, no significant ***education*** × ***brain*** PC ($\beta = 0.01$, s.e. = 0.02, $P = 0.60$) or ***education*** × ***brain*** PC × time ($\beta = 0.004$, s.e. = 0.004, $P = 0.43$) interactions were observed. This means that the relationship between ***brain*** and memory, and the relationship between ***brain*** changes and memory changes, did not vary as a function of ***education*** (Fig. 6b,c), contrary to the prediction from the ***cognitive*** reserve theory.

Replication analyses

The main analyses were run using the alternative categorization of ***education*** (more/less than high school) and a different ***brain*** component derived using machine learning—that is, a regularized regression model (least absolute shrinkage and selection operator (LASSO)) used to predict memory based on an independent sample of 28,114 cross-sectional MRI scans from the UK Biobank, yielding four model specifications (Supplementary Table 8). Controlling for eTIV, cross-sectional ***education***–***brain*** associations were relatively weak although significant at $P < 0.05$ in three models. The ***education*** × time interaction was significant but with small effect sizes in the same three specifications. Effect size was largest for the PC ***brain*** measure and the high school categorization, with an interaction coefficient of 0.008 compared to 0.005 for the two other significant specifications. The ***brain*** × ***education*** × time interaction on memory was not significant in any specification.

As an additional set of control analyses, we tested whether the coefficients for the ***brain*** variables in predicting memory were affected by including ***education*** in the models (Supplementary Fig. 11). The coefficients changed only minimally, suggesting that the ***brain***–memory relationships were largely independent of ***education***.

Discussion

Education was only minimally associated with less ***age***-related ***decline*** in episodic memory and rate of ***decline*** in memory-sensitive ***brain*** regions and did not increase resilience to the ***brain*** changes. The small magnitude of differences in ***brain*** and memory change ***across education*** groups contrasts with the much larger differences in baseline levels, highlighting a distinction between lifelong ***cognitive*** advantages and ***age***-related trajectories.

Additionally, we found evidence that selection effects account for parts of the associations, meaning that people with certain traits, such as larger ***brain*** volumes and higher ***cognitive*** function from early ***age***, were more likely to pursue higher ***education***. This selection process likely varies ***across*** social and demographic contexts and ***educational*** systems. Nevertheless, clear patterns emerged ***across*** diverse samples spanning multiple WEIRD societies and ***age*** ***cohorts***. The findings aligned with trends observed in non-WEIRD societies, suggesting a certain degree of robustness ***across*** populations and historical contexts.

A *role* for *education* in *brain* and *cognitive* *aging*?

The idea that higher ***education*** reduces ***age***-related ***cognitive*** ***decline*** is based on two complementary hypotheses. The first suggests that ***education*** protects against memory ***decline*** by influencing lifestyle factors that help preserve memory-sensitive ***brain*** regions—that is, by promoting ***brain*** maintenance. We found that less ***brain*** atrophy was linked to better episodic memory12, yet differences in ***decline*** trajectories of memory-sensitive ***brain*** regions ***across*** ***educational*** groups were minimal.

This aligns with and extends previous findings16 and provides a neurobiological explanation for why individuals with different ***educational*** attainment experience similar rates of ***age***-related memory decline21,44. An implication is that behaviors associated with higher ***education*** may not be as protective against ***brain*** ***decline***, as often assumed, because we would then expect accumulated effects over time, leading to diverging ***age*** trajectories and different rates of ***brain*** change between ***educational*** groups.

The second hypothesis proposes that ***education*** protects ***cognitive*** function by increasing resilience to ***brain*** ***decline***, building a '***cognitive*** reserve'5,18,19. We found little support for this idea. Differences in ***aging*** trajectories for memory and memory-sensitive ***brain*** regions were minimal, and structural ***brain*** ***decline*** was associated with similar amounts of memory ***decline*** ***across*** ***educational*** levels, aligning with previous research on hippocampal20 and cortical45 atrophy.

Additionally, more ***education*** was not linked to larger re-test effects, suggesting that higher ***education*** did not enhance the ability to benefit from test experience46. Re-test effects reflect the capacity to take advantage of previous testing to improve performance, and, although more ***educated*** individuals encoded new information more effectively—as reflected in their higher memory scores—this did not translate into greater gains from repeated testing. Similar findings have been reported for tests of mental speed and reasoning47.

Taken together, these results suggest that ***education*** does not reduce ***brain*** ***decline*** or episodic memory in ***aging***. Instead, the observed associations likely reflect differences established earlier in life.

How do associations among *brain* volume, *cognitive* function and *education* arise?

The results revealed relationships among ***education***, memory function, slightly larger volumes of memory-sensitive ***brain*** regions and larger intracranial volume. The most straightforward explanation is that individuals with higher ***cognitive*** abilities and larger ***brain*** volumes are more likely to pursue higher education48. Although participants faced unequal opportunities and barriers to education49, which may weaken the link between ***cognitive*** abilities and ***educational*** attainment, the findings suggest that selection may partly explain the associations:

First, consistent with selection effects, participants with higher ***education*** relative to their peers—matched by sex, birth ***cohort*** and ***country***—had better memory function decades later even when accounting for absolute ***education***.

Second, controlling for proxies of childhood ***cognitive*** function and 'scholarly culture'50 attenuated the association between ***education*** and memory performance. Earlier-life ***cognitive*** function predicts ***cognitive*** ability and ***brain*** health in aging51,52, limiting opportunities for causal effects of ***education*** beyond adolescence. This conclusion aligns with a systematic review of the effects of ***education*** on dementia risk, which suggested that low ***education*** is more strongly associated with dementia when it reflects ***cognitive*** capacity rather than privilege and when linked to other risk factors ***across*** the lifespan53.

Third, larger intracranial volume confounded the ***education***–memory relationship. Intracranial volume, a proxy for lifetime maximum ***brain*** size54, is often considered a measure of '***brain*** reserve' and is linked to better ***cognitive*** function in ***aging***, even after accounting for ***brain*** pathology55. Because intracranial volume is fully developed before adolescence, it is unlikely to be directly influenced by ***education***.

Taken together, these findings suggest that earlier-life factors contribute to the lifelong associations between ***education*** and cognition. Still, these observations do not preclude the possibility of causal effects. ***Cognitive*** training can lead to improvements in memory and ***brain*** structure, even in older adults56, 57–58, and early ***education*** could similarly contribute to increased ***brain*** volumes of the magnitude observed here. Because part of the relationship between cognition and ***education*** can be explained by neuroanatomical differences from early childhood33, ***brain*** structure may serve as a phenotype in the causal pathway linking genetic variation to differences in ***cognitive*** function and ***educational*** attainment59.

However, training-induced effects on ***brain*** structure tend to be more transient than those on cognition60,61, making it less likely that direct effects of youth ***education*** on ***brain*** volume would persist into old ***age***. Accordingly, a study found no evidence of structural ***brain*** differences resulting from the increase in mandatory schooling in the UK from 15 years to 16 years, when assessed 50 years later62. Instead, intracranial volume has a stronger relationship to ***education*** than gray matter volume33. In fact, the association between ***education*** and intracranial volume was twice as large in the present study as the association with the ***brain*** component, and removing intracranial volume from the model strengthened the memory–***brain*** relationship. This again points to selection effects. Furthermore, it is consistent with genetic evidence63, although it is important to note that, despite ***education*** and ***cognitive*** function being genetically correlated64, some of the predictive power of polygenic scores for these traits reflects environmental amplification of the genetic effects, which vary ***across*** environments64,65.

Nonetheless, ***education*** could lead to improved ***cognitive*** scores without detectable ***brain*** structure effects. Natural experiments suggest impacts of ***education*** on ***cognitive*** function26, 27–28, including memory23, 24–25, although such effects could reflect improvements in test-taking skills rather than changes in ***brain*** structure or ***cognitive*** functions outside the testing environment21. Such effects could contribute to reductions in early dementia diagnoses, as recently shown in a study of the 1972 UK school reform66, without necessarily reducing ***brain*** pathology. However, it would be surprising for the relationship between ***education*** and memory test performance to remain linear if test-taking skills were the main factor, as improvements would likely plateau at some point. Hence, test-taking skills are unlikely to be the major contributor to the superior memory performance in highly ***educated*** individuals.

The importance of childhood factors

The most coherent interpretation of the current results is that any positive effect of ***education*** on cognition in ***aging*** must stem from early schooling29. The parallel memory–***education*** associations ***across*** the ***age*** range align with evidence that ***education*** enhances lifelong ***cognitive*** function without mitigating ***age***-related ***decline***. Still, most ***cognitive*** intervention studies have found that the positive effects on ***cognitive*** scores diminish over time21,67. Thus, any early effect of ***education*** on cognition would likely need to be sustained through some mechanisms that help maintain the initial benefits.

This idea aligns with the gravitational hypothesis, which suggests that the stability of individual differences in cognition is shaped by consistent exposure to the same environments over time, including social, ***educational*** and economic contexts21,68,69. Studies have shown that '***cognitive*** stimulation' in the workplace is associated with a lower risk of dementia diagnosis70, although it does not fully account for the link between ***education*** and reduced risk71. Furthermore, individuals with higher ***cognitive*** function may naturally seek out ***cognitively*** stimulating activities, regardless of their formal ***education***.

The linear association between memory performance and ***education*** is interesting. If ***education*** directly causes higher ***cognitive*** scores, one might expect diminishing returns with increasing years of schooling. This question has not been adequately addressed by quasi-experimental methods29 and could reflect additive selection effects

across the spectrum of ***educational*** levels. It is also noteworthy that this pattern holds ***across*** diverse samples from many ***countries*** and ***cohorts***, suggesting robustness to societal variations.

Considerations and future research

Although we did not specifically examine variations ***across*** time31 or societies32, ***33***–34, other studies have found relatively consistent ***education***–cognition associations72, in line with our comparisons with ***countries*** in Africa, Latin America and East and South Asia. SHARE employed probability sampling, but the MRI samples are generally less representative73. Although it is difficult to estimate the impact of this, we note that the relationships were replicated in the ***brain*** imaging ***cohorts***.

Test scores correlate with important real-life indicators, such as work participation and independent living, but it remains unclear to what extent differences in scores reflect daily life function66. ***Education*** could improve test scores with minimal effect on the underlying ***cognitive*** construct, especially in crystallized or domain knowledge-based tests, but maybe less so in fluid tasks such as list recall21, although effects have been reported for compound (for example, the *g*-factor) measures of cognition29. One study found that the relationship between ***education*** and ***cognitive*** scores, after controlling for childhood cognition, involved direct effects on specific ***cognitive*** skills, including memory, rather than being mediated by the *g*-factor74. Still, we observed similar associations ***across*** several ***cognitive*** domains. Finally, although structural ***brain*** change is predictive of memory ***decline*** in aging75, other measures could reveal different relationships.

Conclusion

In this large-scale, geographically diverse ***longitudinal*** mega-analytic study, we found that ***education*** is related to better episodic memory and larger intracranial volume and modestly to memory-sensitive ***brain*** regions. These associations are established early in life and not driven by slower ***brain aging*** or increased resilience to structural ***brain*** changes. Therefore, effects of ***education*** on episodic memory function in ***aging*** likely originate earlier in life.

Methods

The research complies with all relevant ethical regulations, and all participants provided informed consent. The main project was approved by the Norwegian Regional Committee for Medical Research Ethics South (approval no. 8122), and each substudy was approved by the relevant ethical review board, as specified in Supplementary Table 3.

Samples

SHARE *cohort*

SHARE is a research infrastructure for studying the effects of health, social, economic and environmental policies over the life course of European citizens and beyond (*https://share-eric.eu/)39*. SHARE contains observations of individuals from 50 years of ***age*** from 28 ***countries***, recruited to be representative of the population in each ***country***. Data for the present analyses were extracted from *easy*SHARE release 8.0.0 (10 February 2022, *https://doi.org/10.6103/SHARE.easy.800);* see refs. 76,77 for methodological details. *easy*SHARE release 8.8.0 is based on SHARE waves 1, 2, 3, 4, 5, 6, 7 and 8 (*https://doi.org/10.6103/SHARE.w1.800*, *https://doi.org/10.6103/SHARE.w2.800*, *https://doi.org/10.6103/SHARE.w3.800*, *https://doi.org/10.6103/SHARE.w4.800*, *https://doi.org/10.6103/SHARE.w5.800*, *https://doi.org/10.6103/SHARE.w6.800*, *https://doi.org/10.6103/SHARE.w7.800*, *https://doi.org/10.6103/SHARE.w8.800)39,78*. Participants included in the analyses participated in up to six waves of data collection. In total, we included data from 130,880 participants (mean ***age*** 64.9 years at baseline, 50.1–112.0, 59,363 males and 71,517 females), with an average of 2.7 waves (s.d. = 1.63) with a mean maximum follow-up interval of 6.53 years (0.9–15.9, s.d. = 3.93). In total, 352,953 memory test sessions were included, with two test results (immediate versus delayed recollection) for each—that is, 705,906 memory scores went into the analyses. Respondents ***aged*** younger than 50 years (individuals recruited due to being spouses of other participants) were

excluded from the sample. An overview of the ***age*** distribution per ***country*** is provided in Fig. 1a. Sample distribution as a function of timepoints, ***education*** category and ***age*** is provided in Supplementary Fig. 3.

Memory was assessed with a 10-word verbal recall test. The word list is read out loud to the participants, and then recall is tested immediately after the presentation (recall 1) and then after a delay of approximately 5 minutes (recall 2). Multiple versions of the lists are assigned to the respondents41. The response distribution is shown in Supplementary Fig. 4. There were no ceiling effects, which is important when assessing ***longitudinal*** change for the best-performing participants. There were some floor effects for recall 2 but less for recall 1, suggesting that we can estimate ***longitudinal*** chance well for most baseline levels of memory. Because ***education*** is associated with differences in memory scores, ceiling and floor effects could potentially obscure real differences in change, but this is unlikely to have affected the current results given the response distribution below. Scores were lower for delayed than immediate recall (odds ratio = 0.535, confidence interval: 0.534–0.537), and females scored higher than males (odds ratio = 1.160, confidence interval: 1.153–1.168).

In addition to the memory measures, we extracted the variables ***age***, sex, birth year, ***education*** (based on the ISCED 1997) and ***country*** of current residency.

MRI *cohorts*

We combined data from 13 datasets with ***longitudinal*** ***brain*** MRI scans and memory assessments: LCBC79, Betula80,81, UB82,83, BASE-II84,85 and Cam-CAN86 datasets (from the Lifebrain consortium)40 as well as the COGNORM87, the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu)88, BBHI89, the Harvard ***Aging*** ***Brain*** Study (HABS)90, the UK Biobank (https://www.ukbiobank.ac.uk/)91, PREVENT-AD92,93, OASIS3 (https://sites.wustl.edu/oasisbrains/)94 and VETSA95. Sample size was maximized for each analysis and, hence, varies due to data availability and missingness (see Supplementary Table 2 for an overview). In addition to ***cohort***-specific inclusion and exclusion criteria, participants older than 50 years without ***cognitive*** impairment, Alzheimer's dementia or severe neurological or psychiatric disorders were included. Additionally, MRI data from scanners with fewer than 15 measurements were also excluded. The initial dataset included individuals with 1–14 MRI acquisitions with ***longitudinal*** structural MRI data spanning up to 15.8 years. Similarly, memory assessments range from one to 24 observations per individual with a follow-up up to 28 years. For detailed descriptions of general characteristics of each dataset, see the study-specific citations above. An overview of each dataset is given in Supplementary Information (Supplementary Table 1). The main sample descriptives are provided in Extended Data Table 2, but because the exact sample size varies somewhat between analyses depending on data availability, the specific characteristics for the samples used and their ***age*** distributions used to address the different research questions are provided in Supplementary Table 2 and Supplementary Fig. 1.

Education **in the** ***brain*** **imaging** ***cohorts***

For each dataset, ***education*** was categorized as high or low using a mean split. We chose this approach because quantitative distributions of ***education*** were often highly non-Gaussian, and level-based codifications were somewhat arbitrary due to idiosyncratic reporting of years of ***education*** and variations in schooling systems ***across*** years and ***country***. To ensure robustness, we conducted analyses with an alternative operationalization of ***education***, categorizing individuals with or without tertiary ***education***. When ***education*** data were provided as qualifications or categories, these were converted to years of ***education*** based on ***country***-specific norms. Individuals were then grouped as having high or low ***education*** based on the median. For the tertiary ***education*** categorization, the reverse process was applied, converting years of ***education*** into ***education*** qualifications. For reporting consistency, a lower cap of 6 years and an upper cap of 20 years were applied to ***education*** years. An overview of ***education*** characteristics for each MRI sample is provided in Supplementary Table 4 and Supplementary Fig. 2.

Memory function in the *brain* imaging *cohorts*

For each sample, we operationalized memory performance as a *z*-normalized score based on the first timepoint and the different available memory tests. When multiple scores were available, we used the first component of a

PCA with all measures as inputs. For each dataset, we regressed out ***age*** (as a smoothing term), sex and one or two dummy test–re-test regressors using GAMMs ('gamm4' R package)43. Individual identifiers were used as random intercepts, and the number of dummy test–re-test regressors depended on whether the dataset had two or three or more waves with memory function data. The residuals were used as an estimate of memory function in each observation. An overview of tests included in the memory performance score for each dataset is provided in Supplementary Table 5.

MRI acquisition and preprocessing

Structural T1-weighted (T1w) MPRAGE and FSPGR scans were collected using 1.5T and 3T MRI scanners. Information regarding scanners and scanner parameters ***across*** datasets are presented in Supplementary Table 6. We used the ***longitudinal*** FreeSurfer version 7.1.0 stream96 for cortical reconstruction and volumetric segmentation of the structural T1w scans97, 98–99. For sessions with multiple scans, data from the scanners were averaged. In brief, the images were processed using the cross-sectional stream, which includes the removal of non-***brain*** tissues, Talairach transformation, intensity correction, tissue and volumetric segmentation, cortical surface reconstruction and cortical parcellation. Next, an unbiased within-subject template space based on all cross-sectional images was created for each participant, using robust, inverse-consistent registration. The processing of each timepoint was then reinitialized with common information from the within-subject template to increase reliability and statistical power. Except for the Betula dataset, all data were preprocessed on the Colossus processing cluster, part of the Services for Sensitive Data (*https://www.uio.no/tjenester/it/forskning/sensitiv/*), University of Oslo. Memory-sensitive ***brain*** measures for each observation were derived using regional loadings based on the 'Destrieux' (cortical)100 and 'aseg' (subcortical) atlases101.

Memory-sensitive *brain* measures

We computed two complementary measures of ***brain*** structure sensitive to memory, capturing different aspects of memory function in older ***age***. The primary measure was defined as a ***longitudinal brain*** component sensitive to memory changes inspired by Vidal-Piñeiro et al. (in preparation). The second measure, for the purpose of assessing the robustness of the results, was trained on independent scans to detect cross-sectional ***brain***–memory relationships in ***aging***. The components were highly correlated ($r = 0.71$), both decrease with ***age*** ($r = -0.67$ and $r = -0.64$, respectively) and include partially overlapping sets of ***brain*** regions. The first measure (***brain*** PC) is optimized to be sensitive to memory changes in ***aging***, whereas the second (***brain*** LASSO) is optimized to detect also offset (that is, baseline) associations. See Supplementary Information for a full description of LASSO.

Brain **PC as a change-based, memory-sensitive measure**

This measure was derived from a sample largely overlapping with that used for the statistical analyses and the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing in the present work but included participants down to ***age*** older than 18 years. ***Brain*** PC is based on a PC of ***longitudinal*** change in 20 cortical thickness and nine subcortical volume regions. ***Brain*** regions were harmonized using a normative modeling framework102,103 with the PCNtoolkit (0.30.post2) in the Python3 environment104 (version 3.9.5). This framework offers several advantages: (1) it is run independently ***across*** sites; (2) it can isolate site effects from other sources of variance associated with it; and (3) it produces site-agnostic deviation scores (z-statistics) adjusted for ***age*** and sex. PCNtoolkit uses a hierarchical Bayesian regression (HBR) technique105 and pretrained models from 82 different datasets, including UK Biobank and Cam-CAN data. To avoid losing ***longitudinal*** observations, we performed this step recursively by iteratively ($n = 100$) holding out a calibrating sample and computing the estimates on the remaining data. The average scores of all iterations were used as the standardized scores for each observation. Scanners contributing with fewer than 12 unique individuals or fewer than 25 observations were excluded. For scanners contributing more than 12 and fewer than 32 unique individuals, we used a calibration sample consisting of all but two participants and estimate the harmonized scores in these two. For scanners with 32 or more unique individuals, we used, in each iteration, a held-out sample of 30 individuals while estimates were applied on the rest.

Next, we selected individuals with at least two observations and a minimum follow-up of 1.5 years. For both MRI and memory preprocessed data, we estimated yearly change for each participant by regressing data on follow-up time. Change data were then fed into separate linear mixed models as implemented in lme4 and lmerTest106,107, one per ***brain*** region. Note that here we used estimates of change, and there was only one observation per individual. For each region, we predicted memory change by ***brain*** change, using dataset as random intercepts. Additionally, we used weights to account for potential heteroskedasticity. That is, individuals with short follow-up periods and fewer observations contribute with more unreliable, high-variance data and, thus, should produce an unequal spread of residuals. We used the square of reliability as weights as estimated in ref. 108. ***Longitudinal*** reliability is a function of variance in change and mean measurement error for a given region and number of observations and total follow-up time for a given individual. After FDR correction ($P < 0.05$), 29 regions showed significant associations between ***brain*** change and memory change, including nine volumetric subcortical regions (bilateral amygdala, hippocampus and thalamus, left lateral and inferior lateral ventricle and right accumbens area) and 20 cortical thickness regions (left G cingul-Post-dorsal, G cingul-Post-ventral, G insular_short, G oc-temp_med-Parahip, G front_inf-Opercular, G front_inf-Triangul, G subcallosal, S temporal_sup; right G Ins lg&S cent_ins, S circular_insula_ant, S oc-temp_med&Lingual, S suborbital; bilateral G temp_sup-Plan_polar, S orbital-H_Shaped, S front_middle, S circular_insula_inf). These regions were entered into the PCA to extract the PC of the memory-sensitive ***brain*** regions, yielding a ***brain*** measure sensitive to episodic memory change in ***aging***. All regions except the ventricles showed positive loadings with the ***brain*** PC.

Statistics

SHARE

Analyses were performed in R (mostly version 4.2.1 (ref. 109)) using the brms package's110 interface to the probabilistic programming language Stan111. To assess effects of ***education*** on memory and memory change, we ran logistic regressions with memory recall as dependent variable, yielding odds ratios as the most relevant model parameter to interpret. An odds ratio of 1 corresponds to a regression coefficient of 0. The main model was:

formula=recalllltrials (10) ~ test + mo (past_tests) + sex + ***country*** + edu + time_since_baseline_z:edu + s(***age***_at_baseline_z,bs="cr") + time_since_baseline_z + ***age***_at_baseline_z:time_since_baseline_z + (1|***country***/mergeid)

Each memory test was used as a separate response, yielding two observations per timepoint, and the variable 'test' represents difficulty of condition 2 relative to condition 1. To control for practice effects, a monotonic function of the number of previous tests taken was included as covariate. We used a smooth function of ***age*** to allow nonlinear relationships. Individual-specific intercepts per participant were nested within ***country***. Default priors were used for all parameters, and two parallel chains of Stan's No-U-Turn Sampler112 were run for 1,500 iterations, discarding the first 1,000 as warmup. This yielded 1,000 post-warmup samples. For the offset/level analyses, ***education*** (edu) was the variable of interest, whereas, for the slope/change analyses, edu × time since baseline was the critical variable. *z*-transformed variables were used in the model fitting for numerical stability, and results were converted back to their natural units for easier interpretability—for example, ***age*** and time in years.

MRI *cohorts*

All the analyses were performed using the R environment (version 4.2.1)109. Visualizations were made with the 'ggplot2'113 and 'ggseg'114 R packages. Memory, ***brain*** variables and eTIV were *z*-standardized before inclusion in the models. Outlier values defined as values >5 s.d. from the mean were removed from the analyses. Analyses were run using GAMM models as implemented in the 'gamm4' R package43, unless otherwise specified.

Memory score was modeled as a function of ***education***, time since baseline, sex and a dummy regressor for test–re-test effects as fixed effects. Baseline ***age*** by sex was included as a smooth term. Random intercepts were modeled per participant and dataset, with random slopes of re-test effects and time from baseline at a dataset level. To test the effects on memory change, the model was re-run with an additional ***education*** × time interaction term. ***Education*** was operationalized either as mean-split or based on tertiary ***education*** in separate models.

Brain structure was modeled as a function of ***education***, time since baseline, sex and eTIV as fixed effects. Baseline ***age*** by sex was included as a smooth term. Random intercepts were modeled per participant, scanner and dataset with random slopes of time included at a dataset level. To test effects on ***brain*** change, the model was re-run with an additional ***education*** × time interaction term. As control analyses, we re-ran the GAMM models without eTIV as covariate. Additionally, we ran a linear mixed model as implemented in lme4, with eTIV being modeled as a function of ***education***, sex and baseline ***age*** as fixed effects, and site and dataset were included as random intercepts. Only the first observation of each participant was included, as eTIV and ***education*** are time-invariant variables. Alternative operationalizations of ***education*** and ***brain*** structure were tested in separate, but otherwise identical, models.

We used a fuzzy join algorithm, as implemented in 'fuzzyjoin'115, to link pairwise MRI and ***cognitive*** observations, as these were not necessarily collected on the same day. MRI observations were matched with the closest ***cognitive*** observations within a maximum time gap of 1 year. Unlinked observations were excluded from the analyses. The relationship among ***brain***, memory level and ***education*** was assessed with several models. '***Brain*** level and memory level': Memory was modeled by ***brain*** structure, sex, time, eTIV and a dummy regressor for test–re-test effects as fixed effects. Baseline ***age*** by sex was introduced as a smooth term. Random intercepts were modeled per participant, scanner and dataset with random slopes of re-test and time modeled at a dataset level. '***Brain*** change and memory change': An additional ***brain*** × time term was added to the model. 'Moderating effect of ***education*** on level–level associations': Additional terms for ***education*** and ***education*** × ***brain*** were added in the first model. 'Moderating effect of ***education*** on change–change associations': A triple interaction term (***brain*** × time × ***education***) as well as its lower-order components were added in the first model. 'Control analyses': A main ***education*** term, without any interaction, was added to the models to assess level–level and change–change associations between ***brain*** and memory, to test whether the strength of these associations was affected by ***education*** level. As with other analyses, alternative operationalizations of ***education*** and memory-sensitive ***brain*** structure were tested in separate but similar models.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03828-y.

Acknowledgements

The Lifebrain consortium is funded by EU Horizon 2020 grant agreement number 732592 (Lifebrain). The different substudies are supported by different sources. LCBC is supported by the European Research Council under grant agreement numbers 283634 and 725025 (to A.M.F.) and number 313440 (to K.B.***W***.) as well as the Norwegian Research Council (325878 and 262453 to A.M.F.; 325001, 301395 and 239889 to K.B.***W***.; 249931 to A.M.F. and K.B.***W***.; 324882 to D.V.-P.; 325415 to H.G.); the National Association for Public Health's Dementia Research Program, Norway (to A.M.F.); and the University of Oslo through the UiO:Life Science convergence environment (to A.M.F.). Betula is supported by a scholar grant from the Knut and Alice Wallenberg Foundation to L.N. Barcelona is partially supported by a Spanish Ministry of Economy and Competitiveness grant to D.B.-F. (grant no. PID2022–137234OB-100 (AEI/FEDER, UE)) and to G.C. and J.S. (grant no. PID-2022–139298OA-C22 (MCIN /AEI /10.13039/501100011033 / FEDER, UE)); by the Walnuts and Healthy ***Aging*** Study (grant no. NCT01634841), funded by the California Walnut Commission, Sacramento, California; and by ICREA Academia 2019 and 2024 awards. BASE-II has been supported by the German Federal Ministry of ***Education*** and Research under grant numbers 16SV5537, 16SV5837, 16SV5538, 16SV5536K, 01UW0808, 01UW0706, 01GL1716A and 01GL1716B and by the European Research Council under grant agreement number 677804 (to S.K.). A.P.-L. is partly supported

by grants from the National Institutes of Health (NIH) (R01AG076708), the Jack Satter Foundation and the BrightFocus Foundation. Part of the research was conducted using the UK Biobank resource under application number 32048. The funders had no ***role*** in study design, data collection and analysis, preparation of the manuscript or decision to publish. L.O.***W***. is funded by the South-Eastern Norway Regional Health Authorities (no. 2017095), by the Norwegian Health Association (no. 19536 and no. 1513) and by Wellcome Leap's Dynamic Resilience Program (jointly funded by Temasek Trust) (no. 104617). Parts of the data used in preparation of this article were obtained from the Pre-Symptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease (PREVENT-AD) program. Data were provided, in part, by OASIS-3 (OASIS-3 principal investigators: T. Benzinger, D. Marcus and J. Morris; NIH P50AG00561, P30NS09857781, P01AG026276, P01AG003991, R01AG043434, UL1TR000448 and R01EB009352). Parts of the data collection and sharing for this project were provided by the Cambridge Centre for Ageing and Neuroscience (Cam-CAN). Cam-CAN funding was provided by the UK Biotechnology and Biological Sciences Research Council (grant no. BB/H008217/1), together with support from the UK Medical Research Council and the University of Cambridge. Parts of the data are from VETSA, which is funded by National Institute of ***Aging*** (NIA) R01 grants AG018384, AG018386, AG050595, AG022381 and AG076838. The content is the responsibility of the authors and does not necessarily represent the official views of the NIA, the NIH, the US Department of Veterans Affairs, the US Department of Defense, the National Personnel Records Center, the National Archives and Records Administration, the Internal Revenue Service, the National Opinion Research Center, the National Research Council, the National Academy of Sciences or the Institute for Survey Research. Temple University provided invaluable assistance in the conduct of the Vietnam Era Twin Registry. The Cooperative Studies Program of the US Department of Veterans Affairs provided financial support for development and maintenance of the Vietnam Era Twin Registry. We would also like to acknowledge the continued cooperation and participation of the members of the Vietnam Era Twin Registry and their families. Part of the data collection and sharing was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (NIH grant U01 AG024904) and DOD ADNI (Department of Defense award no. W81XWH-12–2–0012). The ADNI is funded by the NIA and the National Institute of Biomedical Imaging and Bioengineering and through generous contributions from the following: AbbVie, the Alzheimer's Association; the Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol Myers Squibb; CereSpir, Inc.; Cogstate; Eisai, Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche, Ltd. and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO, Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development, LLC; Lumosity; Lundbeck; Merck & Co., Inc.; MesoScale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals; Pfizer, Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (*https://fnih.org/*). The grantee organization is the Northern California Institute for Research and ***Education***, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Parts of the data used in the preparation of this article were obtained from the Harvard ***Aging Brain*** Study (HABS - P01AG036694; *https://habs.mgh.harvard.edu*). The HABS was launched in 2010, funded by the NIA, and is led by principal investigators R. A. Sperling and K. A. Johnson at Massachusetts General Hospital/Harvard Medical School. The SHARE data collection has been funded by the European Commission, DG RTD through FP5 (QLK6-CT-2001-00360), FP6 (SHARE-I3: RII-CT-2006-062193, COMPARE: CIT5-CT-2005-028857, SHARELIFE: CIT4-CT-2006-028812), FP7 (SHARE-PREP: GA no. 211909, SHARE-LEAP: GA no. 227822, SHARE M4: GA no. 261982, DASISH: GA no. 283646) and Horizon 2020 (SHARE-DEV3: GA no.; 676536, SHARE-COHESION: GA no. 870628, SERISS: GA no. 654221, SSHOC: GA no. 823782, SHARE-COVID19: GA no. 101015924) and by DG Employment, Social Affairs & Inclusion through VS 2015/0195, VS 2016/0135, VS 2018/0285, VS 2019/0332, VS 2020/0313, SHARE-EUCOV: GA no. 101052589 and EUCOVII: GA no. 101102412. Additional funding from the German Federal Ministry of ***Education*** and Research (01UW1301, 01UW1801, 01UW2202), the Max Planck Society for the Advancement of Science, the NIA (U01_AG09740-13S2, P01_AG005842, P01_AG08291, P30_AG12815, R21_AG025169, Y1-AG-4553-01, IAG_BSR06-11, OGHA_04-064, BSR12-04, R01_AG052527-02, R01_AG056329-02, R01_AG063944, HHSN271201300071C, RAG052527A) and various national funding sources is gratefully acknowledged (see *https://www.share-eric.eu/*).

Notes

Extended datais available for this paper at https://doi.org/10.1038/s41591-025-03828-y.Supplementary informationThe online version contains supplementary material available at https://doi.org/10.1038/s41591-025-03828-y.**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Classification

Language: ENGLISH

Publication-Type: Magazine

Journal Code: 41591

Subject: DIAGNOSTIC IMAGING (78%); POPULATION GROWTH (87%); DEMENTIA (89%); ***BRAIN*** (91%); ADULTS (70%); MAGNETIC RESONANCE IMAGING (71%); MEMORY DISORDERS (89%); INTELLIGENCE & COGNITION (90%); SOCIETY, SOCIAL ASSISTANCE & LIFESTYLE (89%); ***AGING*** (91%); INVESTIGATIONS (74%); POPULATION & DEMOGRAPHICS (78%); MEMORY (91%); BEHAVIOR & COGNITION (78%); SENIOR CITIZENS (78%)

Organization: Center for Lifespan Changes in ***Brain*** and Cognition, University of Oslo; Computational Radiology and Artificial Intelligence, Department of Radiology and Nuclear Medicine; Oslo University Hospital; Ragnar Frisch Centre for Economic Research; Department of Medicine; Faculty of Medicine and Health Sciences, Institute of Neurosciences, University of Barcelona; Institut Guttmann, Institut Universitari de Neurorehabilitació adscrit a la UAB; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); Center for Lifespan Psychology, Max Planck Institute for Human Development; Department of Psychology; MSB Medical School Berlin; Max Planck UCL Centre for Computational Psychiatry and Ageing Research; Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol; MRC Cognition and ***Brain*** Sciences Unit, Department of Psychiatry; University of Cambridge; Center for Environmental Neuroscience, Max Planck Institute for Human Development; Department of Psychiatry and Psychotherapy; University Medical Center Hamburg-Eppendorf; Department of Sociology and

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Industry: DIAGNOSTIC IMAGING (78%); MAGNETIC RESONANCE IMAGING (71%)

Geographic: BERLIN, GERMANY (79%); HAMBURG, GERMANY (79%)

Load-Date: July 28, 2025
