



Influence of young adult cognitive ability and additional education on later-life cognition

William S. Kremen^{a,b,c,1}, Asad Beck^{b,d}, Jeremy A. Elman^{a,b}, Daniel E. Gustavson^{a,b}, Chandra A. Reynolds^e, Xin M. Tu^{b,f}, Mark E. Sanderson-Cimino^{a,b,d}, Matthew S. Panizzon^{a,b}, Eero Vuoksima^g, Rosemary Toomey^h, Christine Fennema-Notestine^{a,b,i}, Donald J. Hagler Jr.^{a,b,i}, Bin Fang^{a,b}, Anders M. Dale^{a,b,i,j}, Michael J. Lyons^h, and Carol E. Franz^{a,b,1}

^aDepartment of Psychiatry, University of California, San Diego, La Jolla, CA 92093; ^bCenter for Behavior Genetics of Aging, University of California, San Diego, La Jolla, CA 92093; ^cCenter of Excellence for Stress and Mental Health, VA San Diego Healthcare System, La Jolla, CA 92161; ^dDepartment of Psychology, San Diego State University, San Diego, CA 92182; ^eDepartment of Psychology, University of California, Riverside, CA 92521; ^fDepartment of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA 92093; ^gInstitute for Molecular Medicine Finland, University of Helsinki, 00014 Helsinki, Finland; ^hDepartment of Psychological and Brain Sciences, Boston University, Boston, MA 02215; ⁱDepartment of Radiology, University of California, San Diego, La Jolla, CA 92093; and ^jDepartment of Neurosciences, University of California, San Diego, La Jolla, CA 92093

Edited by Sarah-Jayne Blakemore, Institute of Cognitive Neuroscience, University College London, London, United Kingdom, and accepted by Editorial Board Member Michael S. Gazzaniga December 8, 2018 (received for review July 4, 2018)

How and when education improves cognitive capacity is an issue of profound societal importance. Education and later-life education-related factors, such as occupational complexity and engagement in cognitive-intellectual activities, are frequently considered indices of cognitive reserve, but whether their effects are truly causal remains unclear. In this study, after accounting for general cognitive ability (GCA) at an average age of 20 y, additional education, occupational complexity, or engagement in cognitive-intellectual activities accounted for little variance in late midlife cognitive functioning in men age 56–66 ($n = 1009$). Age 20 GCA accounted for 40% of variance in the same measure in late midlife and approximately 10% of variance in each of seven cognitive domains. The other factors each accounted for <1% of the variance in cognitive outcomes. The impact of these other factors likely reflects reverse causation—namely, downstream effects of early adult GCA. Supporting that idea, age 20 GCA, but not education, was associated with late midlife cortical surface area ($n = 367$). In our view, the most parsimonious explanation of our results, a meta-analysis of the impact of education, and epidemiologic studies of the Flynn effect is that intellectual capacity gains due to education plateau in late adolescence/early adulthood. Longitudinal studies with multiple cognitive assessments before completion of education would be needed to confirm this speculation. If cognitive gains reach an asymptote by early adulthood, then strengthening cognitive reserve and reducing later-life cognitive decline and dementia risk may really begin with improving educational quality and access in childhood and adolescence.

cognitive aging | longitudinal | occupational complexity | cognitive activities | reverse causation

Education, occupational complexity, and later life engagement in cognitive-intellectual activities are generally considered to be protective against risk for dementia (1–6). They are also frequently used as indices of cognitive reserve (7); for example, higher education is associated with greater resistance to Alzheimer's disease (AD) pathology (4, 8). However, such putative protective effects for promoting or maintaining brain and cognitive function could indicate reverse causation, that is, people with higher intellectual capacity attaining higher levels of education and occupational complexity and engaging more frequently in intellectually stimulating activities (9–11). Reverse causation is also consistent with the substantial genetic association between education and general cognitive ability (GCA), and the relationship of education to midlife and later-life cognitive function is largely mediated by genetic influences on GCA (12, 13). (Here we use GCA to refer to any IQ-like summary or principal component index of overall cognitive function.) Some studies also have found that additional education increases intelligence (14, 15), but whether this means

that additional education-related exposures at any age—particularly later in life—will improve cognition is unclear.

Here we focus primarily on studies with cognitive data from earlier age periods, because these were able to test reverse causation and provide the most precise estimates. A meta-analysis of seven studies (10 datasets) with pre-post comparisons found that each additional year of education accounted for an average of 1.20 additional later-life IQ points (14). The average increase in IQ points per year of education was 2.06 in policy change studies (e.g., increasing compulsory education) and 5.22 points in studies comparing students entering school at different ages. On the other hand, there is also evidence for an end, and even a partial reversal,

Significance

The impact of additional education on later-life cognition remains unclear. After accounting for general cognitive ability (GCA) at age 20 y, education, occupational complexity, or engagement in cognitive-intellectual activities accounted for <1% of the variance in late midlife cognitive functioning. Age 20 y GCA, but not education, was also associated with late midlife cortical surface area. Education exposures likely reflect reverse causation, that is, downstream effects of earlier GCA. Education does improve cognitive ability, but there are suggestions that this effect plateaus in late adolescence/early adulthood. If so, improving educational quality and access much earlier in life may be important for reducing later-life cognitive decline and risk for dementia.

Author contributions: W.S.K., M.S.P., R.T., C.F.-N., D.J.H., A.M.D., M.J.L., and C.E.F. designed research; W.S.K., M.S.P., R.T., C.F.-N., D.J.H., A.M.D., M.J.L., and C.E.F. performed research; W.S.K., A.B., J.A.E., D.E.G., C.A.R., X.M.T., E.V., B.F., and C.E.F. analyzed data; X.M.T. oversaw statistical analysis; X.M.T. and B.F. completed implementation and write-up of the multiple test correction procedure; M.S.P. contributed critical comments/edits; C.E.F. collaborated on developing the idea/model for the paper; and W.S.K., A.B., J.A.E., D.E.G., C.A.R., M.E.S.-C., and E.V. wrote the paper.

Conflict of interest statement: A.M.D. is a founder of and holds equity in CorTechs Labs, Inc. and serves on its scientific advisory board. He is also a member of the scientific advisory board of Human Longevity, Inc. and receives funding through research agreements with GE Healthcare and Medtronic. The terms of these arrangements have been reviewed and approved by University of California, San Diego in accordance with its conflict of interest policies. The remaining authors declare no competing interests.

This article is a PNAS Direct Submission. S.-J.B. is a guest editor invited by the Editorial Board.

Published under the PNAS license.

Data deposition: Data are available at the The Vietnam Era Twin Study of Aging (VETSA) website, <https://medschool.ucsd.edu/som/psychiatry/research/VETSA/Pages/default.aspx>.

See Commentary on page 1832.

¹To whom correspondence may be addressed. Email: wkremen@ucsd.edu or cfranz@ucsd.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1811537116/-DCSupplemental.

Published online January 22, 2019.

of the Flynn effect—i.e., secular increases in IQ associated with increasing education in later cohorts—in late adolescence (16, 17).

Clouston et al. (18) assessed cognition at age 15–16 y in three cohorts. These data were included in the meta-analysis, but they specifically addressed the benefit of a university education. Completing a university education led to a midlife gain of 0.39–1.49 SD, equivalent to gains of 6–22.35 IQ points over adolescent cognitive ability compared with individuals who did not attend university. Scottish cohort studies are particularly valuable because they include identical pretests and posttests of GCA. There was an increase equivalent to 1.42 and 0.66 IQ points per year of education in the Lothian 1936 (at age 70 y) and 1921 (at age 79 y) birth cohorts, respectively, after controlling for age 11 GCA (19). After controlling for age 11 GCA in the 1936 cohort, social-intellectual activity accounted for an average of 0.25–2.85% of the variance in reading recognition, processing speed, and memory (10); physical activity accounted for an average of 0.49–2.25% of the variance in these cognitive abilities. After accounting for age 11 GCA and age 79 y brain burden measures in the Aberdeen cohort, education accounted for an average of 6.0% of the variance in memory but none of the variance in reasoning (20). Occupation accounted for an average of 4.2% of the variance in memory and 6.7% of the variance in reasoning.

Whether additional education or other factors affect midlife or late-life cognitive function beyond what was accounted for by earlier-life GCA warrants further study for several reasons. The magnitude of effects differs substantially across studies. Most studies covered composite indices or limited cognitive measures, and almost all had different pretest and posttest measures. In addition, putative protective factors were generally examined one at a time. Such models may miss significant predictors and may be biased (21). Simultaneous examination would be useful because these factors are related to one another.

Given evidence of the impact of education on later cognition being largely mediated by genetic influences on GCA, and for the leveling off of the Flynn effect in studies of late adolescents, our primary hypothesis was that education, occupational complexity, and midlife engagement in cognitive-intellectual activities would contribute little to late-midlife cognitive functioning over and above GCA assessed post-high school in young adulthood. We simultaneously examined several other factors that have been associated with later-life cognitive function (22), assessed education at baseline testing as well as lifetime educational attainment, and examined outcomes in seven cognitive domains plus the same test of GCA that had been administered more than four decades earlier. In previous work, we showed that cortical surface area, but not thickness, is associated with GCA, and that this association remains stable over the lifespan (23, 24). Therefore, we also hypothesized that age 20 GCA, but not lifetime education or cortical thickness, would be positively associated with late-midlife cortical surface area. Consistent with reverse causation, extremely little variance in late-midlife cognition was accounted for by the other factors after accounting for earlier GCA. In addition, getting a 4-y university education after the baseline assessment accounted for virtually no variance in late-midlife GCA after accounting for baseline GCA. Again, consistent with reverse causation, our hypothesis about cortical surface area was also supported.

Materials and Methods

Participants. The study participants were subjects in the Vietnam Era Twin Study of Aging (VETSA), which has been described in detail previously (25, 26). Participants were recruited from a registry of twins serving in the American military at some point between 1965 and 1975 (27). Eligibility for VETSA 1 included age 51–59 y at enrollment and both members of a twin pair agreeing to participate. VETSA 2 was conducted 5.69 (SD = 0.69) y later. Nearly 80% of participants reported no combat exposure. The sample is reasonably representative in that the participants are similar in health and lifestyle characteristics to American men in their age range (28). Of the 1,237 individuals who participated in VETSA 1, 1,009 (82%) returned for VETSA 2. Neuroimaging was instituted midway into the VETSA project; 367 participants had valid neuroimaging data. All participants provided written informed consent. The study was approved by Institutional Review Boards at

the University of California, San Diego, Boston University, and Massachusetts General Hospital.

Measures.

Childhood socioeconomic status (cSES). cSES was calculated using highest parental education and occupation during childhood (<18 y) based on the Hollingshead Scale (29).

Age 20 education. This is the highest attained years of formal education when participants took the test of GCA at an average age of 20 y.

Age 20 and 62 GCA. At an average age of 20 y and at VETSA 2 (average age, 62 y), participants took the Armed Forces Qualification Test (AFQT) (30). The AFQT has a high correlation with other tests of GCA (31, 32). AFQT percentile scores underwent probit transformation for analysis to normalize the distribution (*SI Appendix, Materials and Methods*).

Lifetime education. This is the highest attained years of formal education over one's lifetime.

Measures at VETSA 1 (Average Age, 56 y). More details are provided in *SI Appendix, Materials and Methods and Table S1*. Correlations among the predictor variables (cSES, age 20 GCA, and VETSA 1 measures) are shown in *SI Appendix, Table S1*.

Occupational complexity. Occupational complexity refers to the highest level of occupation attained according to the International Standard Classification of Occupations (ISCO) (33). There are 10 major groups, from managers/leaders/major professionals (coded as 1) to elementary occupations, such as laborers/drivers (coded as 9).

Engagement in cognitive-intellectual activities. We used a composite score of 11 self-reported activity items during the past month on the Life Complexity Inventory (34), which provides information about the frequency of engagement in cognitively stimulating activities in one's free time. One point was assigned for each activity based on participant engagement.

Physical activity. Participants reported frequency of engagement in physical fitness and walking/hiking during the past month using a 5-point Likert scale, ranging from "never" to "daily." The measure was the average of both categories.

Health status. Health was measured according to a modification of the Charlson Comorbidity Index (35). One point was assigned for the presence of 15 different chronic medical conditions. Higher scores indicate poorer health.

Measures at VETSA 2 (Average Age, 62 y).

Cognitive domains. Seven cognitive domains were derived from 23 scores from 13 neuropsychological tests administered during VETSA 2 (36, 37). For domains with multiple tests and scores, we calculated the mean of z-scored measures except for executive function, which was based on a common factor (38). Higher scores represent better performance. The domains were abstract reasoning, episodic memory, processing speed, verbal fluency, visual-spatial ability, working memory, and executive (*SI Appendix, Methods and Table S2*). Correlations among the cognitive outcome measures are shown in *SI Appendix, Table S3*.

Magnetic resonance imaging. Total cortical surface area and mean cortical thickness measures were derived using FreeSurfer 5.1 with T1-weighted images acquired on 3-T scanners at two data collection sites. Acquisition parameters, editing, and quality control procedures have been described in detail elsewhere (39–42) (*SI Appendix, Materials and Methods*).

Statistical Analysis. More details are provided in *SI Appendix, Materials and Methods*.

Mixed-model analysis. All variables were standardized (mean = 0; SD = 1). Type III effects are presented. We ran models 1–4 for each cognitive outcome plus age 62 GCA; model 5 was for age 62 GCA only. The six models were as follows:

Model 1: Predictors were cSES, lifetime education, occupational complexity, engagement in cognitive-intellectual activities, physical activity, and health.

Model 2: Model 1 predictors plus age 20 education. Collinearity diagnostics using the variance inflation factor statement in SAS 9.4 PROC REG indicated that this model with 2 measures of education was valid.

Model 3: Model 1 predictors plus age 20 GCA.

Model 4: Model 3 with only participants with exactly 12 y of education at the time of the age 20 GCA assessment.

Model 5: Model 4 participants but with lifetime education dichotomized into groups with 12 y versus 16+ y. Here we examined age 62 GCA as the only outcome with cSES and age 20 GCA as the only other predictors to provide a comparison with Clouston et al. (18) on the effect of a university education on later GCA.

Model 6: Models with only a single additional protective factor (6a, lifetime education; 6b, occupational complexity).

To correct for multiple tests and for correlations among the outcome measures, we applied the method of Li and Ji (43) to the false discovery rate (SI Appendix, Materials and Methods and Table S3).

Magnetic Resonance Imaging Analyses. We previously showed that surface area, rather than thickness, drove the cortical–GCA association in VETSA 1 (23). Here we examined the correlations of lifetime education and age 20 GCA with total cortical surface area and mean cortical thickness at age 62 y.

Co-Twin Control Analyses. We used a co-twin control design to evaluate whether observed associations of education with cognitive outcomes showed evidence of a direct causal effect, after controlling for genetic and familial/shared environmental effects (44, 45). Because the contribution of education was so small (Results), we report the co-twin control data in SI Appendix, Results.

Covariates and Other Statistical Adjustments. Before entry into all analyses, measures were adjusted for age at VETSA 2 and race/ethnicity (white non-Hispanic vs. other). We controlled for correlated twin pair data using random effects in all but the co-twin control analyses. Magnetic resonance imaging analyses included a covariate for scanner because two different scanners were used.

Results

Sample Characteristics. Participant age range was 51–60 y at the VETSA 1 assessment and 56–66 y at the VETSA 2 assessment. The participants were primarily non-Hispanic white (89%) and currently married (78%). When the age 20 GCA measure was administered, 92% had completed high school and 22% had attained some college education. For lifetime education, 97% had completed high school, 60% had some college education, and 29% had a bachelor's degree or higher. The average percentile score on the age 20 GCA measure was 61.48, which corresponds to an IQ of approximately 104–105. More sample characteristic details are provided in SI Appendix, Materials and Methods, Results, and Tables S4 and S5.

Mixed Models That Examined Multiple Protective Factors.

Model 1. As shown in Table 1, after multiple testing correction, lifetime education was a significant predictor of six of seven cognitive domains plus age 62 GCA. Occupational complexity and cognitive-intellectual activities were each significant predictors of five cognitive domains, and health was significantly associated with four domains plus GCA. Physical activity was a significant predictor of only one cognitive domain.

Model 2. Here we added education at age 20 y as a predictor (SI Appendix, Table S6). After multiple testing correction, education

at age 20 y did not contribute to any cognitive outcomes. Contributions of the other predictors were similar to the results for model 1.

Model 3. Here we included age 20 GCA in place of age 20 education. As shown in Table 2, age 20 GCA was by far the strongest predictor, significant for all later cognitive measures. Again, results for the other predictors were similar to the results for models 1 and 2. The median percentage of variance in specific cognitive abilities that was accounted for by lifetime education, occupational complexity, and cognitive-intellectual activities was 0.77%, 0.71%, and 0.45%, respectively. The median percentage of variance in specific cognitive abilities accounted for by age 20 GCA was 10.24%.

Model 4. Here we improved precision because the participants' educational level was identical (12 y) at the time they took the test of GCA. After multiple testing correction, age 20 GCA contributed significantly to age 62 GCA and all specific cognitive abilities except verbal fluency (Table 3). Lifetime education was no longer a significant predictor of any cognitive measure, and the number of other significant predictors was reduced substantially compared with models 1–3.

Model 5. Here we included age 20 GCA and dichotomized lifetime education (12 y vs. 4-y university education) with age 62 GCA as the outcome and cSES as the only other predictor ($n = 463$; SI Appendix, Table S7). Age 20 GCA accounted for 40% of the variance in age 62 GCA; education accounted for 1.60%. In models 3 and 4, with education as a continuous variable, age 20 GCA accounted for 39% and 40% of the variance in age 62 GCA, respectively, and education accounted for nearly none of the variance. For the 12-y education group, GCA was 0.002 SD higher at age 62 y than at age 20 y, and for the university education group, GCA was 0.084 SD higher at age 62 y than at age 20 y. The difference between the two groups is equivalent to a 1.23-IQ point gain from having at least a university education (<0.308 per year).

Mixed Models That Examined only a Single Protective Factor (Models 6a and 6b).

With a less stringent multiple testing correction in these models, both lifetime education and occupational complexity were significantly associated with all specific cognitive abilities and age 62 GCA after adjusting for age 20 GCA (SI Appendix, Table S8). Lifetime education accounted for a median of 1.90% of the variance in the different cognitive abilities, 1.44% of the variance in occupational complexity, and 11.09–12.25% of the variance in age 20 GCA. Including age and ethnicity as covariates had little impact on these results. Age 20 GCA accounted

Table 1. Model 1: Predictors of late midlife (average age 62 y) cognitive function including lifetime education

Cognitive ability/domain	Childhood SES	Age 20 y education	Lifetime education	Occupational complexity	Engagement in cognitive activities	Physical activity	Health status
Age 62 y GCA ($n = 963$)	0.046; $P = 0.223$	—	0.121; $P = 0.001$	0.036; $P = 0.265$	0.123; $P = 0.00033$	−0.051; $P = 0.106$	−0.076; $P = 0.013$
Abstract reasoning ($n = 964$)	0.094; $P = 0.009$	—	0.121; $P = 0.001$	0.080; $P = 0.015$	0.107; $P = 0.002$	−0.074; $P = 0.022$	−0.106; $P = 0.00049$
Episodic memory ($n = 965$)	0.011; $P = 0.779$	—	0.149; $P = 0.000038$	0.083; $P = 0.010$	0.088; $P = 0.010$	−0.025; $P = 0.417$	−0.036; $P = 0.238$
Processing speed ($n = 962$)	0.040; $P = 0.274$	—	0.082; $P = 0.030$	0.120; $P = 0.0004$	0.099; $P = 0.005$	0.026; $P = 0.43$	−0.081; $P = 0.010$
Verbal fluency ($n = 963$)	0.002; $P = 0.968$	—	0.156; $P = 0.000019$	0.068; $P = 0.038$	0.137; $P = 0.000058$	0.000; $P = 0.997$	0.001; $P = 0.969$
Visual-spatial ability ($n = 956$)	0.066; $P = 0.079$	—	0.110; $P = 0.003$	0.061; $P = 0.053$	0.123; $P = 0.00030$	−0.027; $P = 0.390$	−0.073; $P = 0.015$
Short-term/working memory ($n = 964$)	0.049; $P = 0.200$	—	0.143; $P = 0.000060$	0.088; $P = 0.006$	0.031; $P = 0.348$	−0.012; $P = 0.702$	−0.037; $P = 0.214$
Executive function ($n = 966$)	0.061; $P = 0.104$	—	0.147; $P = 0.000028$	0.100; $P = 0.002$	0.029; $P = 0.375$	−0.026; $P = 0.396$	−0.072; $P = 0.015$

Engagement in cognitive activities, physical activity, and health status were assessed at average age 56 y. All outcomes were adjusted for age and race/ethnicity. Numbers in the table are β coefficients. Values in bold type are significant after correction for multiple testing. Sample sizes are 93–96% of the total number. Exact P values are shown to highlight differences in magnitude of effects. SES, socioeconomic status.

Table 2. Model 3: Predictors of late midlife (average age 62) cognitive function including age 20 GCA and lifetime education

Cognitive ability/domain	Childhood SES	Age 20 y GCA	Lifetime education	Occupational complexity	Engagement in cognitive activities	Physical activity	Health status
Age 62 y GCA (n = 948)	−0.025; <i>P</i> = 0.364	0.638; <i>P</i> = 1.1e-82	0.015; <i>P</i> = 0.606	0.030; <i>P</i> = 0.256	0.055; <i>P</i> = 0.045	−0.013; <i>P</i> = 0.612	−0.064; <i>P</i> = 0.009
Abstract reasoning (n = 949)	0.053; <i>P</i> = 0.112	0.355; <i>P</i> = 2.2e-28	0.057; <i>P</i> = 0.103	0.078; <i>P</i> = 0.013	0.068; <i>P</i> = 0.039	−0.048; <i>P</i> = 0.116	−0.099; <i>P</i> = 0.00059
Episodic memory (n = 950)	−0.020; <i>P</i> = 0.593	0.273; <i>P</i> = 1.9e-16	0.106; <i>P</i> = 0.004	0.085; <i>P</i> = 0.008	0.055; <i>P</i> = 0.102	−0.011; <i>P</i> = 0.724	−0.029; <i>P</i> = 0.331
Processing speed (n = 947)	0.021; <i>P</i> = 0.569	0.203; <i>P</i> = 2.3e-09	0.049; <i>P</i> = 0.189	0.119; <i>P</i> = 0.00035	0.071; <i>P</i> = 0.042	0.044; <i>P</i> = 0.177	−0.074; <i>P</i> = 0.017
Verbal fluency (n = 948)	−0.018; <i>P</i> = 0.629	0.127; <i>P</i> = 0.0014	0.138; <i>P</i> = 0.00017	0.072; <i>P</i> = 0.028	0.124; <i>P</i> = 0.00029	0.009; <i>P</i> = 0.774	0.006; <i>P</i> = 0.855
Visual-spatial ability (n = 941)	0.020; <i>P</i> = 0.553	0.408; <i>P</i> = 2.1e-37	0.048; <i>P</i> = 0.159	0.059; <i>P</i> = 0.049	0.074; <i>P</i> = 0.019	0.006; <i>P</i> = 0.842	−0.067; <i>P</i> = 0.017
Short-term/working memory (n = 949)	0.011; <i>P</i> = 0.763	0.328; <i>P</i> = 1.2e-23	0.095; <i>P</i> = 0.007	0.085; <i>P</i> = 0.005	−0.009; <i>P</i> = 0.791	0.011; <i>P</i> = 0.725	−0.025; <i>P</i> = 0.386
Executive function (n = 951)	0.014; <i>P</i> = 0.683	0.320; <i>P</i> = 2.0e-23	0.101; <i>P</i> = 0.004	0.106; <i>P</i> = 0.0004	−0.011; <i>P</i> = 0.735	−0.004; <i>P</i> = 0.906	−0.066; <i>P</i> = 0.020

Engagement in cognitive activities, physical activity, and health status were assessed at average age 56 y. All outcomes were adjusted for age and race/ethnicity. Numbers in the table are β coefficients. Values in bold type are significant after correction for multiple testing. Sample sizes are 93–96% of the total number. Exact *P* values are shown to highlight differences in the magnitude of effects. GCA, general cognitive ability; SES, socioeconomic status.

for 41–43% of the variance in age 62 GCA, and education accounted for <1%.

Associations with Cortical Surface Area and Thickness at Age 62 y.

Lifetime education was unrelated to either total cortical surface area ($\beta = 0.034$; $P < 0.4829$; $r = 0.03$; $n = 365$) or mean cortical thickness ($\beta = 0.001$; $P < 0.9830$; $r \sim 0.00$; $n = 367$). Age 20 GCA was significantly correlated with cortical surface area ($\beta = 0.167$; $P < 0.0009$, $r = 0.158$; $n = 357$) but not with mean cortical thickness ($\beta = 0.031$; $P < 0.5224$; $r = 0.03$; $n = 359$). The age 20 GCA-surface area association remained significant even when restricting the analysis to only individuals with exactly 12 y of education ($\beta = 0.143$; $P < 0.0171$; $r = 0.130$; $n = 223$).

Discussion

The most parsimonious explanation of our results is reverse causation—namely, that individuals with higher intellectual capacity tend to attain more education, achieve higher occupational status, and engage more in cognitive-intellectual activities. Thus, the impact of the latter factors is primarily downstream of intellectual capacity. On average, after accounting for age 20 GCA,

lifetime education or occupational complexity each accounted for <1% of variance in specific cognitive abilities. In contrast, age 20 GCA accounted for ~10% on average. For participants with exactly the same amount of education at baseline testing, differences in additional education still had little impact on later cognitive function. Supporting these results, age 20 GCA—but not education—was associated with age 62 cortical surface area, a finding consistent with the documented stability of brain-GCA associations (24). Active gene-environment correlation—that is, individuals genetically predisposed to higher intellectual ability tending to seek out environments that promote cognitive and brain development (46, 47)—may account in part for this phenomenon.

The two Lothian birth cohorts provide the best comparison with our study because within studies, each used the same test at outcome and at baseline. In the two Lothian cohorts, there was an equivalent of a 0.66-IQ point and 1.42-IQ point advantage, respectively, for each year of education (weighted average, 1.18) in their models with age 11 GCA, education, and cSES. In our comparable model (*SI Appendix, Table S8*), education resulted in a 0.33-IQ point per year gain for age 62 GCA. With 12 y of education, one would expect an increase of >14 IQ points based

Table 3. Model 4: Predictors of late midlife (average age 62 y) cognitive function including age 20 y GCA and lifetime education (including only participants with exactly 12 y of education at the age 20 y GCA assessment)

Cognitive ability/domain	Childhood SES	Age 20 y GCA	Lifetime education	Occupational complexity	Engagement in cognitive activities	Physical activity	Health status
Age 62 GCA (n = 663)	−0.047; <i>P</i> = 0.148	0.645; <i>P</i> = 2.1e-55	0.021; <i>P</i> = 0.570	0.060; <i>P</i> = 0.054	0.079; <i>P</i> = 0.018	0.041; <i>P</i> = 0.189	−0.092; <i>P</i> = 0.002
Abstract reasoning (n = 662)	0.049; <i>P</i> = 0.222	0.324; <i>P</i> = 9.2e-17	0.021; <i>P</i> = 0.646	0.072; <i>P</i> = 0.050	0.087; <i>P</i> = 0.029	0.023; <i>P</i> = 0.544	−0.114; <i>P</i> = 0.001
Episodic memory (n = 663)	−0.007; <i>P</i> = 0.875	0.269; <i>P</i> = 7.7e-12	0.074; <i>P</i> = 0.101	0.062; <i>P</i> = 0.086	0.066; <i>P</i> = 0.095	0.014; <i>P</i> = 0.707	0.007; <i>P</i> = 0.832
Processing speed (n = 662)	0.015; <i>P</i> = 0.733	0.173; <i>P</i> = 0.000020	0.035; <i>P</i> = 0.462	0.134; <i>P</i> = 0.00040	0.109; <i>P</i> = 0.009	0.086; <i>P</i> = 0.028	−0.075; <i>P</i> = 0.044
Verbal fluency (n = 663)	−0.029; <i>P</i> = 0.522	0.096; <i>P</i> = 0.020	0.101; <i>P</i> = 0.034	0.063; <i>P</i> = 0.097	0.132; <i>P</i> = 0.002	0.061; <i>P</i> = 0.116	−0.005; <i>P</i> = 0.902
Visual-spatial ability (n = 658)	0.023; <i>P</i> = 0.570	0.409; <i>P</i> = 6.8e-27	0.092; <i>P</i> = 0.035	0.056; <i>P</i> = 0.104	0.077; <i>P</i> = 0.043	0.034; <i>P</i> = 0.341	−0.075; <i>P</i> = 0.024
Short-term/working memory (n = 663)	0.015; <i>P</i> = 0.743	0.318; <i>P</i> = 1.2e-15	0.095; <i>P</i> = 0.036	0.095; <i>P</i> = 0.008	0.023; <i>P</i> = 0.551	0.059; <i>P</i> = 0.110	−0.033; <i>P</i> = 0.348
Executive function (n = 664)	0.004; <i>P</i> = 0.918	0.305; <i>P</i> = 1.4e-15	0.084; <i>P</i> = 0.055	0.131; <i>P</i> = 0.00013	−0.005; <i>P</i> = 0.896	0.043; <i>P</i> = 0.226	−0.084; <i>P</i> = 0.014

Engagement in cognitive activities, physical activity, and health status were assessed at average age 56 y. All outcomes were adjusted for age and race/ethnicity. Numbers in the table are β coefficients. Values in bold type are significant after correction for multiple testing. Sample sizes are 93–96% of the total number. Exact *P* values are shown to highlight differences in magnitude of effects. GCA, general cognitive ability; SES, socioeconomic status.

on the Lothian studies vs. <4 points based on the VETSA study. In cohorts examined by Clouston et al. (18), the gain from having a university over a high school education was 6–22.35 IQ point equivalents, compared with only 0.40 point in VETSA. Cohort differences do not seem likely to account for the lower education-related gain in VETSA. One would expect quality of education, health, and nutrition—all of which contribute to cognitive and brain development—to be better in later-born cohorts, but education-associated gains were largest in the earlier-born cohorts. Country—United States, England, or Scotland—also did not account for the differences. It is also worth noting that only these studies with the same baseline and outcome tests can provide measures of absolute education-related IQ point gains. All other analyses can provide only a rough approximation by standardizing scores for different baseline and outcome tests.

With average age at baseline testing of 12.35 y in the meta-analysis, there was an average gain of 1.20 IQ points per year of education in pre-post studies and 2.06 IQ points per year in policy change studies (14). The authors suggested that IQ gains might diminish with increasing education rather than being additive across multiple years of education. If additive, the lower estimate of 1.20 would translate to a 14.40-point increase for 12 y of education and a 24-point increase with 4 y of university education plus 4 y of graduate school. Such continued substantial increases seem implausible. In fact, we speculate that the lower gain in our sample is because baseline testing was done at a much later age. There is still substantial brain development during childhood and adolescence. Additional education likely provides an enriching environment that promotes brain and cognitive development; however, by age 20 y there would be much less subsequent brain development (48, 49). With that in mind, it is noteworthy that despite similar stability coefficients, in the Lothian birth cohorts there was a substantial increase of 1.12–1.51 SDs in mean GCA from age 11 y to age 70 or 79 y (19); in the VETSA, there was virtually no change—a 0.08 SD increase—from age 20 y age 62 y. A Norwegian policy change study showed that additional schooling in adolescence raised IQs, but left open the question of whether that trend would continue with later education (15). Based on testing at age 18–19 y, other Norwegian population studies have shown that the Flynn effect—increasing IQ with increasing compulsory education—has leveled off and even slightly reversed (16, 17). Those findings are also consistent with education-associated IQ gains eventually plateauing, perhaps reaching an asymptote by age 18–19 y.

The inclusion of multiple additional predictors in our models might explain the smaller amounts of variance accounted for by education or occupational complexity compared with other studies. After accounting for age 20 GCA in VETSA models without the additional predictors, education and occupational complexity contributed an average of 1.90% and 1.44% of variance, respectively, in later specific cognitive abilities (*SI Appendix, Table S8*), compared with <1% in model 3 with additional covariates (Table 2). Thus, within a study, the effect of education is likely to be inflated when other relevant and correlated predictors are not accounted for. On the other hand, comparable analyses still resulted in smaller education-associated gains from later baseline testing in the VETSA compared with the Lothian cohorts.

The well-known education-associated reduction in risk for mild cognitive impairment (MCI) and AD also may be primarily attributable to reverse causation. In previous work with the present sample, individuals diagnosed with MCI—when based on age- and education-adjusted scores without adjusting for age 20 GCA—had lower age 20 GCA than cognitively normal participants (50). Higher AD polygenic risk scores were associated with significantly increased odds of having MCI in our sample, supporting our MCI diagnosis as being AD-related (51). In a large Danish study, baseline GCA assessed in early adulthood (age 19–30 y) predicted later dementia, and education had no effect after accounting for baseline GCA (52).

One implication of our results is that studies examining educational activities and cognitive training in older adults should include random assignment to conditions to rule out reverse causation. Cognitive training in later life can be beneficial for remediating declines and supporting maintenance of functioning, although transfer of training has been inconsistent (53–58). However, evidence of late adolescent/early adult plateauing of the effects of education on cognitive ability suggests limited effects of later life education-related activities. Consistent with that idea, successful programs in older adults seem to require intensive intervention of relatively long duration (54–58). Early life factors, such as low birth weight, low cSES, and poverty, already have substantial effects on brain development and GCA (24, 59), but these effects are potentially modifiable. Thus, in some ways, reducing the risk of later cognitive decline may begin early in life.

Strengths and Limitations. Strengths of this study include the extensive coverage of cognitive domains, use of the same baseline and outcome GCA measures, simultaneous examination of multiple predictors, and additional analyses in which all participants had identical educational levels at baseline. Limitations include reduced generalizability due to the all-male, predominantly white, non-Hispanic sample. We also lacked fine-grained measures of physical activity and health status. The effects of occupational complexity, cognitive activities, and physical activity might have been stronger had they been based on longer time frames, but that could also increase memory inaccuracy. Moreover, 6-y correlations for cognitive activities and physical activity of 0.644 and 0.545 suggest that the 1-mo time frame does provide reasonable stability. Despite strong epidemiologic evidence for a leveling out of education-related IQ gains by late adolescence, we are unable to definitively confirm our hypothesis regarding possible sensitive periods for brain development and the age of baseline testing. Such confirmation would require testing at multiple time points before the completion of education all within the same study. We did not see evidence of significant differential effects on different cognitive abilities, but it is also difficult to draw firm conclusions, because no studies had the same specific ability measures at baseline and outcome.

Summary. Reverse causation appears to be the primary explanation for the associations of education, occupational complexity, and cognitive-intellectual activities with better later-life cognitive functioning and their possible link to a reduced risk of MCI or dementia. These factors are likely to be largely downstream effects of early-adult general intellectual capacity. Thus, caution is warranted when interpreting their impact or their use as indices of reserve. Because these factors are correlated, each of which may have small effects on later-life cognitive functioning, examining only one factor at a time may inflate its apparent effect. There is evidence that education does help enhance cognitive abilities, but our data are consistent with epidemiologic data suggesting a plateauing of those effects by late adolescence/early adulthood. The need for formal testing of this hypothesis remains, however. The leveling-off phenomenon is consistent with data suggesting that education-related activities in later life must be very intensive to have meaningful effects. It may also suggest that a reduction in later-life cognitive decline and dementia risk actually might begin with improving earlier educational quality and access.

ACKNOWLEDGMENTS. We acknowledge the continued cooperation and participation of the members of the Vietnam Era Twin (VET) Registry and their families. The Cooperative Studies Program of the US Department of Veterans Affairs (VA) provides financial support for development and maintenance of the VET Registry. The content of this article is the responsibility of the authors and does not necessarily represent official views of the National Institute on Aging, the National Institutes of Health, or the VA. This work was supported by National Institute on Aging Grants R01 AG050595 (to W.S.K., M.J.L., and C.E.F.), R01 AG022381 and R01AG022982 (to W.S.K.), R03AG046413 (to C.E.F.), and K08AG047903 (to M.S.P.), and Juho Vainio Foundation and Academy of Finland Grant 314639 (to E.V.). W.S.K. was also supported by the VA San Diego Center of Excellence for Stress and Mental Health Healthcare System.

- Boots EA, et al. (2015) Occupational complexity and cognitive reserve in a middle-aged cohort at risk for Alzheimer's disease. *Arch Clin Neuropsychol* 30:634–642.
- Dekhtyar S, Wang H-X, Fratiglioni L, Herlitz A (2016) Childhood school performance, education and occupational complexity: A life-course study of dementia in the Kungsholmen project. *Int J Epidemiol* 45:1207–1215.
- Dekhtyar S, et al. (2015) A life-course study of cognitive reserve in dementia—From childhood to old age. *Am J Geriatr Psychiatry* 23:885–896.
- Stern Y (2012) Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* 11:1006–1012.
- Wang H-X, MacDonald SWS, Dekhtyar S, Fratiglioni L (2017) Association of lifelong exposure to cognitive reserve-enhancing factors with dementia risk: A community-based cohort study. *PLoS Med* 14:e1002251.
- Lee ATC, et al. (2018) Association of daily intellectual activities with lower risk of incident dementia among older Chinese adults. *JAMA Psychiatry* 75:697–703.
- Vuoksimaa E, et al. (2016) Middle age self-report risk score predicts cognitive functioning and dementia in 20–40 years. *Alzheimers Dement (Amst)* 4:118–125.
- Barulli D, Stern Y (2013) Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends Cogn Sci* 17:502–509.
- Stine-Morrow EAL, Basak C (2011) Cognitive interventions. *Handbook of the Psychology of Aging*, eds Schaie KW, Willis SL (Academic, San Diego), 7th Ed, pp 153–171.
- Gow AJ, Corley J, Starr JM, Deary IJ (2012) Reverse causation in activity-cognitive ability associations: The Lothian Birth Cohort 1936. *Psychol Aging* 27:250–255.
- Corley J, Cox SR, Deary IJ (2018) Healthy cognitive ageing in the Lothian Birth Cohort studies: Marginal gains not magic bullet. *Psychol Med* 48:187–207.
- Pedersen NL, Reynolds CA, Gatz M (1996) Sources of covariation among mini-mental state examination scores, education, and cognitive abilities. *J Gerontol B Psychol Sci Soc Sci* 51:55–63.
- Carmelli D, Swan GE, Cardon LR (1995) Genetic mediation in the relationship of education to cognitive function in older people. *Psychol Aging* 10:48–53.
- Ritchie SJ, Tucker-Drob EM (2018) How much does education improve intelligence? A meta-analysis. *Psychol Sci* 29:1358–1369.
- Brinch CN, Galloway TA (2012) Schooling in adolescence raises IQ scores. *Proc Natl Acad Sci USA* 109:425–430.
- Sundet JM, Barlaug DG, Torjussen TM (2004) The end of the Flynn effect? A study of secular trends in mean intelligence test scores of Norwegian conscripts during half a century. *Intelligence* 32:349–362.
- Bratsberg B, Rogeberg O (2018) Flynn effect and its reversal are both environmentally caused. *Proc Natl Acad Sci USA* 115:6674–6678.
- Clouston SA, et al. (2012) Benefits of educational attainment on adult fluid cognition: International evidence from three birth cohorts. *Int J Epidemiol* 41:1729–1736.
- Ritchie SJ, Bates TC, Der G, Starr JM, Deary IJ (2013) Education is associated with higher later life IQ scores, but not with faster cognitive processing speed. *Psychol Aging* 28:515–521.
- Staff RT, Murray AD, Deary IJ, Whalley LJ (2004) What provides cerebral reserve? *Brain* 127:1191–1199.
- Wang H, et al. (2017) Inconsistency between univariate and multivariate logistic regressions. *Shanghai Arch Psychiatry* 29:124–128.
- Gatz M, Prescott CA, Pedersen NL (2006) Lifestyle risk and delaying factors. *Alzheimer Dis Assoc Disord* 20(Suppl 2):S84–S88.
- Vuoksimaa E, et al. (2015) The genetic association between neocortical volume and general cognitive ability is driven by global surface area rather than thickness. *Cereb Cortex* 25:2127–2137.
- Walhovd KB, et al. (2016) Neurodevelopmental origins of lifespan changes in brain and cognition. *Proc Natl Acad Sci USA* 113:9357–9362.
- Kremen WS, Franz CE, Lyons MJ (2013) VETSA: The Vietnam Era Twin Study of Aging. *Twin Res Hum Genet* 16:399–402.
- Kremen WS, et al. (2006) Genes, environment, and time: The Vietnam Era Twin Study of Aging (VETSA). *Twin Res Hum Genet* 9:1009–1022.
- Eisen S, True W, Goldberg J, Henderson W, Robinette CD (1987) The Vietnam Era Twin (VET) registry: Method of construction. *Acta Genet Med Gemellol (Roma)* 36:61–66.
- Schoenborn CA, Heyman KM (2009) Health characteristics of adults aged 55 years and over: United States, 2004–2007. *Natl Health Stat Report* 16:1–31.
- Hollingshead AB, Redlich FC (1958) *Social Class and Mental Illness: A Community Study* (Wiley, New York).
- Uhlman JE, Bolanovich DJ (1952) Development of the Armed Forces qualification test and predecessor army screening tests, 1946–1950 (Personnel Research Section, Department of the Army, Washington, DC).
- Lyons MJ, et al. (2009) Genes determine stability and the environment determines change in cognitive ability during 35 years of adulthood. *Psychol Sci* 20:1146–1152.
- Lyons MJ, et al. (2017) A longitudinal twin study of general cognitive ability over four decades. *Dev Psychol* 53:1170–1177.
- International Labour Office (2012) *International Standard Classification of Occupations: Structure, Group Definitions, and Correspondence Tables*. ISCO-08 (International Labour Office, Geneva, Switzerland), Vol 1.
- Schaie KW (2005) *Developmental Influences on Adult Intelligence: The Seattle Longitudinal Study* (Oxford Univ Press, New York).
- Charlson M, Szatrowski TP, Peterson J, Gold J (1994) Validation of a combined comorbidity index. *J Clin Epidemiol* 47:1245–1251.
- Beck A, et al. (2018) Mediators of the effect of childhood socioeconomic status on late midlife cognitive abilities: A four-decade longitudinal study. *Innov Aging* 2:igy003.
- Franz CE, et al. (2011) A 35-year longitudinal assessment of cognition and midlife depression symptoms: The Vietnam Era Twin Study of Aging. *Am J Geriatr Psychiatry* 19:559–570.
- Gustavson DE, et al. (2018) Genetic and environmental architecture of executive functions in midlife. *Neuropsychology* 32:18–30.
- Kremen WS, et al. (2010) Genetic and environmental influences on the size of specific brain regions in midlife: The VETSA MRI study. *Neuroimage* 49:1213–1223.
- Eyler LT, et al. (2011) Genetic and environmental contributions to regional cortical surface area in humans: A magnetic resonance imaging twin study. *Cereb Cortex* 21:2313–2321.
- Elman JA, et al. (2017) Genetic and environmental influences on cortical mean diffusivity. *Neuroimage* 146:90–99.
- Hatton SN, et al. (2018) Negative fateful life events in midlife and advanced predicted brain aging. *Neurobiol Aging* 67:1–9.
- Li J, Ji L (2005) Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. *Heredity (Edinb)* 95:221–227.
- Carlin JB, Gurrin LC, Sterne JA, Morley R, Dwyer T (2005) Regression models for twin studies: A critical review. *Int J Epidemiol* 34:1089–1099.
- McGue M, Osler M, Christensen K (2010) Causal inference and observational aging research: The utility of twins. *Perspect Psychol Sci* 5:546–556.
- Plomin R, DeFries JC, Loehlin JC (1977) Genotype-environment interaction and correlation in the analysis of human behavior. *Psychol Bull* 84:309–322.
- Haworth CM, et al. (2010) The heritability of general cognitive ability increases linearly from childhood to young adulthood. *Mol Psychiatry* 15:1112–1120.
- Zahodne LB, Stern Y, Manly JJ (2015) Differing effects of education on cognitive decline in diverse elders with low versus high educational attainment. *Neuropsychology* 29:649–657.
- Johnson SB, Blum RW, Giedd JN (2009) Adolescent maturity and the brain: The promise and pitfalls of neuroscience research in adolescent health policy. *J Adolesc Health* 45:216–221.
- Kremen WS, et al. (2014) Early identification and heritability of mild cognitive impairment. *Int J Epidemiol* 43:600–610.
- Logue MW, et al. (February 27, 2018) Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50s. *Mol Psychiatry*, 10.1038/s41380-018-0030-8.
- Osler M, Christensen GT, Garde E, Mortensen EL, Christensen K (2017) Cognitive ability in young adulthood and risk of dementia in a cohort of Danish men, brothers, and twins. *Alzheimers Dement* 13:1355–1363.
- Hertzog C, Kramer AF, Wilson RS, Lindenberger U (2008) Enrichment effects on adult cognitive development: Can the functional capacity of older adults be preserved and enhanced? *Psychol Sci Public Interest* 9:1–65.
- Motes MA, et al. (2018) Higher-order cognitive training effects on processing speed-related neural activity: A randomized trial. *Neurobiol Aging* 62:72–81.
- Park DC, et al. (2014) The impact of sustained engagement on cognitive function in older adults: The Synapse project. *Psychol Sci* 25:103–112.
- McDonough IM, Haber S, Bischof GN, Park DC (2015) The Synapse project: Engagement in mentally challenging activities enhances neural efficiency. *Restor Neurol Neurosci* 33:865–882.
- Carlson MC, et al. (2015) Impact of the Baltimore Experience Corps Trial on cortical and hippocampal volumes. *Alzheimers Dement* 11:1340–1348.
- Willis SL, et al.; ACTIVE Study Group (2006) Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA* 296:2805–2814.
- Hair NL, Hanson JL, Wolfe BL, Pollak SD (2015) Association of child poverty, brain development, and academic achievement. *JAMA Pediatr* 169:822–829.