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Original Contribution

Impact of Differential Attrition on the Association of Education With Cognitive Change Over 20 Years of Follow-up

The ARIC Neurocognitive Study

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Studies of long-term cognitive change should account for the potential effects of education on the outcome, since some studies have demonstrated an association of education with dementia risk. Evaluating cognitive change is more ideal than evaluating cognitive performance at a single time point, because it should be less susceptible to confounding. In this analysis of 14,020 persons from a US cohort study, the Atherosclerosis Risk in Communities (ARIC) Study, we measured change in performance on 3 cognitive tests over a 20-year period, from ages 48–67 years (1990–1992) through ages 70–89 years (2011–2013). Generalized estimating equations were used to evaluate the association between education and cognitive change in unweighted adjusted models, in models incorporating inverse probability of attrition weighting, and in models using cognitive scores imputed from the Telephone Interview for Cognitive Status for participants not examined in person. Education did not have a strong relationship with *change* in cognitive test performance, although the rate of decline was somewhat slower among persons with lower levels of education. Methods used to account for selective dropout only marginally changed these observed associations. Future studies of risk factors for cognitive impairment should focus on cognitive change, when possible, to allow for reduction of confounding by social or cultural factors.

aging; cognition; cognitive decline; cognitive reserve; education

Abbreviations: ARIC, Atherosclerosis Risk in Communities; GEE, generalized estimating equations; IPAW, inverse probability of attrition weighting; MMSE, Mini-Mental State Examination; TICS, Telephone Interview for Cognitive Status.

Cognitive test performance is strongly influenced by a person's educational level and other cultural factors. Such factors must be accounted for in any study of age-related and disease-related cognitive decline. Change in cognitive performance may be a better outcome for evaluating causes of cognitive impairment than is a measure of cognitive performance at a single time point, because change is less susceptible to confounding by factors that are stable over time within adults. A previous report from the Atherosclerosis Risk in Communities (ARIC) Study showed that education was strongly associated with cross-sectional cognitive performance but not with its change during midlife (1, 2).

Studying risk factors for disease-related long-term cognitive decline requires appropriate modeling. Change may not be linear (3, 4), and trends may be influenced by practice effects or selective dropout, differential relative to exposure (in this case, education). Failing to account for this dropout might lead to aberrant or missed associations.

Prior studies of education and cognitive change have been hindered by sample characteristics, analytic techniques, or limited cognitive assessment (1, 5–13). Here we evaluate the association of education with cognitive change from 1990 to 2013 in black and white men and women aged 47–67 years in the ARIC Study, explore the shape of the trends, and evaluate the influence of selective attrition.

METHODS

Study population

The ARIC Study was a population-based cohort study of 15,792 middle-aged adults from 4 US communities: Washington County, Maryland; Forsyth County, North Carolina; selected suburbs of Minneapolis, Minnesota; and Jackson, Mississippi (black participants only). Participants were seen at 4 study visits from 1987–1989 (ages 45–64 years) through 1996–1998, with a fifth visit (also called the ARIC Neurocognitive Study) in 2011–2013 and annual follow-up telephone calls. Cognitive performance was evaluated in all participants at visit 2 (1990–1992; ages 48–67 years), at visit 4 (1996–1998; ages 54–73 years), and at visit 5 (as part of the ARIC Neurocognitive Study) (2011–2013; ages 70–89 years); it was also evaluated in a subset of participants (Forsyth County and Jackson only) at visit 3 (1993–1995; $n = 1,920$) and in ancillary studies of carotid magnetic resonance imaging (2004–2006; $n = 2,066$) and the brain (2004–2006; $n = 1,130$) (14–16).

Baseline for the current analysis was ARIC visit 2 (1990–1992). We excluded participants who did not attend visit 2, had missing cognitive or educational data, were neither black nor white, or were blacks residents of Washington County or Minneapolis (due to small numbers); this resulted in a sample size of 14,020. The study was approved by each institution's institutional review board.

Education

Education was assessed during visit 1 as the highest grade of schooling completed. It was categorized as less than high school (<12 years), completion of high school or vocational school (12 years), or more than high school (any college/professional school; >12 years).

Cognitive function

Three cognitive tests were administered by trained examiners in a quiet room, in a fixed order: the Delayed Word Recall Test, the Digit Symbol Substitution Test, and the Word Fluency Test. Protocols were standardized. Quality control of examiner performance was monitored by review of audiotaped recordings.

The Delayed Word Recall Test is a test of verbal learning and short-term memory. The participant learns 10 common nouns, uses each in 2 sentences, and, after a 5-minute interval during which another test is given, is asked to recall as many words as possible. The score is the number of nouns correctly recalled (17).

The Digit Symbol Substitution Test is a test of executive function and processing speed. The participant translates numbers to symbols with the help of a key. The score is the number of correct translations within 90 seconds, with a maximum of 93 (18).

The Word Fluency Test is a test of executive function and expressive language. The participant spends 1 minute each generating words beginning with a particular letter, for 3 different letters. The score is the sum of correct words generated for all 3 letters (19).

A z score was calculated for each test score and each visit, separately by race, by subtracting the overall mean test score (from visit 2) from each participant's test score and dividing by the visit 2 standard deviation. A global z score was calculated for each visit by averaging the z scores of the 3 tests and then subtracting the global mean and dividing by its standard deviation (from visit 2).

Statistical analysis

Baseline mean values and proportions for participant characteristics were calculated separately by race and the 3 educational levels. To estimate the association between educational level and rate of cognitive decline over time, we used generalized estimating equations (GEE) linear regression models with an exchangeable correlation structure and robust standard error estimates, which take into account the intraindividual correlation of cognitive test scores at successive visits. The models were stratified by race and included education category, follow-up time (years), follow-up time squared (time^2), age (years, centered at 55), sex, and interactions between these variables.

As described above, the Delayed Word Recall Test, the Digit Symbol Substitution Test, and the Word Fluency Test were administered to all examinees at ARIC visits 2, 4, and 5 (Figure 1) and to subsamples of ARIC participants at visit 3 and the 2 ARIC magnetic resonance imaging ancillary visits. The GEE models described here used only the visit 2, visit 4, and visit 5 test scores. They included all persons who had data for all 3 cognitive tests at visit 2. Random-effects models using test scores from all 5 occasions with random slopes and intercepts produced almost identical findings (not shown).

Compared with the reference education category (more than high school), coefficients for the less-than-high-school and high-school categories reflect differences in mean baseline cognitive test score, adjusted for covariates. Interaction terms for education group × time, which was of primary interest for the current analysis, were used to test the null hypothesis of no difference in cognitive score change over time among education groups. Terms for education group × time^2 were also evaluated but results were not substantial or statistically significant, so they were not included in the final models. As a method that is less sensitive to influential points than

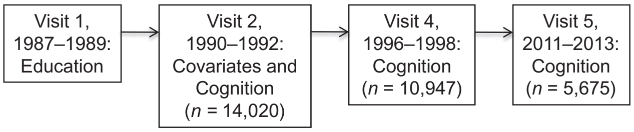

Figure 1. Numbers of persons seen at study visits 2, 4, and 5, Atherosclerosis Risk in Communities Study, 1987–2013.

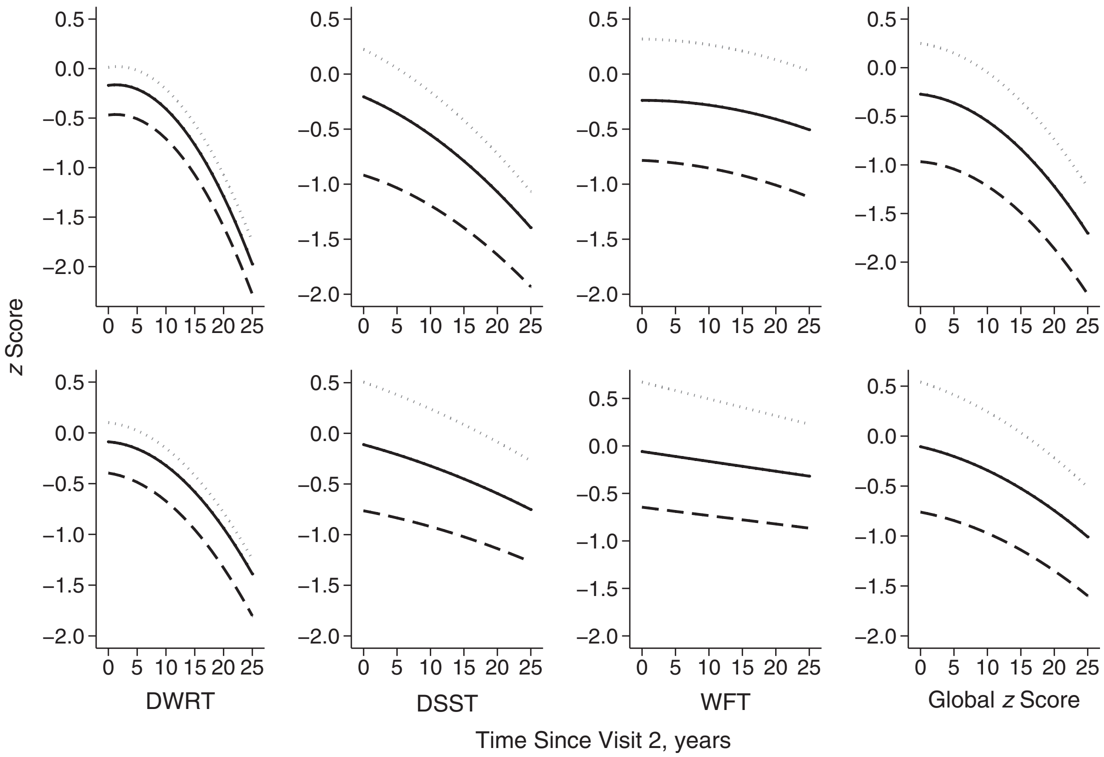

Figure 2. Predicted mean trajectory of cognitive test *z* scores, by race and educational level, for a male aged 55 years at baseline, Atherosclerosis Risk in Communities Study, 1990–2013. Top panels show results for white participants, and bottom panels show results for black participants. Dotted line, more than a high school education; solid line, completion of high school or vocational school; dashed line, less than a high school education. DSST, Digit Symbol Substitution Test; DWRT, Delayed Word Recall Test; WFT, Word Fluency Test.

quadratic modeling, a linear spline analysis was also performed, with knots at 5, 7, and 20 years (20). This gave similar results, providing additional support for the trajectories shown in Figure 2.

Floor effects

To reduce the impact of possible floor effects (21), we repeated the primary analyses after excluding persons in the lowest 5% of scores at baseline within each racial group.

Practice effects

To evaluate possible practice effects, we examined test score differences from visit 2 to visit 3 in the subset of persons who underwent cognitive testing at these visits. To determine whether these differences varied by educational level, we used age- and sex-adjusted linear regression models stratified by race.

Dropout bias

Persons with a low level of education (or other risk factors for cognitive decline) may be more likely to die or to refuse follow-up examinations. If they also differ from other participants in terms of their susceptibility to cognitive decline, the observed associations between education and cognitive decline may be biased (22). We used 2 methods to evaluate and correct for the possible effects of selective attrition: inverse probability of attrition weighting (IPAW) and imputation of missing scores using the Telephone Interview for Cognitive Status (TICS) (23).

Inverse probability of attrition weighting

Using previously reported IPAW methods (22), we developed 2 sets of logistic regression models, one predicting attrition from visit 2 to visit 4 and one predicting attrition from visit 4 to visit 5. Attrition due to mortality and other loss to follow-up (censoring) were modeled separately. Weights were based on the product of the probability of being alive and of remaining in the study for each individual, for each visit.

Models predicting attrition from visit 2 to visit 4 included: hypertension, smoking, global cognitive *z* score, education, age, sex, race/center, diabetes, prevalent coronary heart disease, prevalent stroke, self-reported health, and retirement status. Self-reported health was assessed at visit 1, all other variables at visit 2. The models for attrition from visit 4 to visit 5 included: 1) variables from the previous model, 2) variables assessed at visit 4 (hypertension, smoking, diabetes, prevalent coronary heart disease, and prevalent stroke), and 3) variables from the most recent annual follow-up telephone call prior to visit 5 (self-reported health; number of recent hospitalizations; physician-diagnosed stroke, myocardial

Table 1. Characteristics of Participants by Race and Education, Atherosclerosis Risk in Communities Study, 1990–2013

	Educational Level								
	<HS			HS			>HS		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Whites									
Study visit									
Visit 2	1,694	15.9		4,890	45.9		4,077	38.2	
Visit 4	1,257	14.2		4,059	46.0		3,509	39.8	
Visit 5	461	9.8		2,143	45.7		2,081	44.4	
Female sex	858	15.2		2,915	51.6		1,877	33.2	
Age at visit 2, years			59.3 (5.4)			57.1 (5.6)			56.7 (5.7)
Age at visit 5, years			77.8 (5.5)			76.0 (5.1)			75.5 (5.2)
Mortality after visit 2	639	37.7		1,214	24.8		877	21.5	
Blacks									
Study visit									
Visit 2	1,289	38.4		962	28.6		1,108	33.0	
Visit 4	845	34.7		715	29.3		877	36.0	
Visit 5	405	30.1		391	29.1		549	40.8	
Female sex	819	38.0		642	29.7		696	32.3	
Age at visit 2, years			57.8 (5.7)			55.4 (5.7)			54.9 (5.4)
Age at visit 5, years			76.5 (5.4)			76.5 (5.1)			74.3 (5.0)
Mortality after visit 2	537	41.7		284	29.5		267	24.1	

Abbreviations: HS, high school; SD, standard deviation.

infarction, or heart failure; hospitalization for stroke, myocardial infarction, or heart failure; functional status; and employment status). Attrition was well accounted for in these models, with areas under the curve of 0.78 for death and 0.69 for censoring for visit 4 and 0.84 and 0.73, respectively, for visit 5. The censoring modeled here is for failure to be examined among invited persons.

The weight for visit 4 is the inverse of the product of the probabilities of being alive at visit 4 and of having a cognitive test score at that visit. The weight for individuals at visit 5 is equal to 1/(probability of being alive at visit 4 × probability of having a score at visit 4 × probability of being alive at visit 5 × probability of having a score at visit 5). Our GEE model was weighted as described to evaluate the education and time × education coefficients of interest. We truncated the weights at 20 to reduce the influence of a few large weights. We also calculated stabilized weights (22) by dividing our original weights by weights created using only baseline age, sex, race, and educational level.

TICS imputation

In a secondary analysis, we imputed a global z score for persons who did not attend visit 5 but completed a telephone assessment, the TICS (939 white participants and 98 black participants). The TICS correlates with scores on the modified Mini-Mental State Examination (3MS) (23) and with scores on the standard Mini-Mental State Examination (MMSE) (24), which was administered at visit 5; but individual items differ between the tests. To make them more comparable, we simulated the MMSE score (designated MMSE*) in persons who completed the TICS by subtracting the word recall items (which are not part of the MMSE) and scaled the scores from a maximum of 31 points to 30 points, to match the MMSE. Next we used linear regression to model, in examined persons, their global z score using as predictors visit 5 age, MMSE score, Delayed Word Recall Test score, visit 4 global z score, and educational level. Finally, we used the results of this regression to impute a global z score for nonexamined persons using MMSE* and the Delayed Word Recall Test scores derived from their TICS scores in analyses combining the examined and nonexamined persons. The weighted GEE analysis was performed in SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina), and all other analyses were performed using Stata, version 12 (StataCorp LP, College Station, Texas). Reported P values are 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the 10,661 white participants and 3,359 black participants are shown in Table 1. Among both blacks and whites, persons with less than a high school education were approximately 3 years older than those with an education greater than high school. Mortality was much higher among persons with less than a high school education (37.7% in whites and 41.7% in blacks, as compared with 21.5% in whites and 24.1% in blacks with more than a

Table 2. Mean Cognitive Test Scores by Race and Education, Atherosclerosis Risk in Communities Study, 1990–2013

	Whites			Blacks		
	<HS	HS	>HS	<HS	HS	>HS
Mean global *z* score						
Visit 2	−0.87	−0.05	0.42	−0.69	0.07	0.71
Visit 4	−0.94	−0.16	0.28	−0.69	−0.01	0.63
Visit 5	−1.64	−0.91	−0.46	−1.03	−0.38	0.15
Delayed Word Recall Test						
Visit 2	6.20	6.79	6.99	5.59	6.29	6.56
Visit 4	6.10	6.71	6.90	5.51	6.11	6.51
Visit 5	4.56	5.24	5.52	4.19	5.09	5.30
Digit Symbol Substitution Test						
Visit 2	38.85	48.77	53.21	22.16	32.26	40.51
Visit 4	37.41	46.60	50.58	21.77	31.00	39.13
Visit 5	31.86	39.63	43.17	19.47	27.56	34.53
Word Fluency Test						
Visit 2	26.64	33.51	39.91	19.75	27.82	37.49
Visit 4	26.79	33.41	39.34	20.11	27.71	36.61
Visit 5	25.11	32.03	38.52	19.26	26.97	34.73

Abbreviation: HS, high school.

high school education). Therefore, at visit 5, a smaller proportion of individuals were in the less educated group than at baseline. All test scores (Table 2) were substantially higher for more educated groups, and all scores decreased across visits in each education group so that large differences between groups persisted. Participants who had not attended visit 5 were older, more likely to be male, and had more comorbidity, lower baseline cognitive test scores, and lower educational levels than those who did attend visit 5 (Table 3). At ARIC visit 1, the analytic sample ($n = 14{,}020$) was slightly younger (54.1 years vs. 54.2 years), more likely to be female (55.7% vs. 55.2%), and less likely to be black (24.0% vs. 27.0%) than the full cohort ($n = 15{,}792$) ($P < 0.01$ for each comparison).

The variables included in the primary analysis are shown in Table 4. Adding other covariates to the models (such as hypertension or smoking) did not lead to substantial changes in any coefficients. Persons with lower educational levels had substantially lower baseline test scores. Figure 2 shows the predicted mean scores over time for global *z* scores and each individual test by race among men. As demonstrated by the graph and the significant time and time^2 coefficients (Table 3), cognitive scores declined in a nonlinear manner in all groups. As an example, the 20-year decline in global *z* score among white men at age 55 years (at baseline) was 1.0 among persons with an educational level greater than high school (calculated as $-0.0101 \times 20 + -0.0020 \times 20^2$) and 0.91 among those with an educational level less than high school ($-0.0101 \times 20 + -0.0020 \times 20^2 + 0.0046 \times 20$) (calculating decline as $\beta_1 \times \text{time} + \beta_2 \times \text{time}^2 + \beta_3 \times \text{time}$, with β_1 as the linear time coefficient, β_2 as the time^2 coefficient, and β_3 as the education × time interaction coefficient for less than a high school education). Thus, having a lower level of education was significantly associated ($P = 0.015$) with less decline in global *z* performance, independent of age and sex. For comparable black participants, the mean decline was 0.75 in those with more than a high school education and 0.58 in those with less than a high school education.

Table 5 and Figure 2 show the results from models of change in *z* scores for individual tests. Declines were seen for each test and each group, but declines were steepest and most accelerated for the Delayed Word Recall Test and least steep for the Word Fluency Test. For the Digit Symbol Substitution Test and the global *z* score, smaller cognitive declines were seen among persons with lower educational attainment. However, these patterns were not consistently seen for the Delayed Word Recall Test or the Word Fluency Test.

Weighted analysis

Coefficients changed slightly with IPAW (Table 4), and, as expected, 20-year declines were increased for all groups. Lower educational levels were still associated with less annual decline in the global *z* score, but the differences were small. For the unweighted models, whites with less than a high school education experienced less 20-year decline than whites with more than a high school education by 0.092 global *z* score units. The difference was reduced to 0.058 units in the IPAW-weighted models (with loss of statistical significance). However, blacks with less than a high school education experienced 0.17 fewer units of decline over 20 years than blacks with more than a high school education in unweighted models—virtually the same as the 0.158 difference in the IPAW model.

Models with global *z* score imputed from TICS scores

Only 1,037 nonexamined persons had available TICS scores. Results of models with global *z* score using TICS imputation were altered very little from those of the other models (Table 4). Effects of education on cognitive change remained small.

Practice effects

To evaluate whether practice effects were evident or differed in individuals by educational level, we compared Delayed Word Recall, Digit Symbol Substitution, and Word Fluency test scores over the 3-year interval between visits 2 and 3, when participants may have been young enough to avoid substantial age-related cognitive decline. Some scores improved slightly; others declined, demonstrating no clear pattern of practice effects, and no patterns associated with educational level emerged (Appendix Table 1).

Floor effects

We repeated analyses after excluding persons in the lowest 5% of baseline global *z* scores (Table 6), because of the

Table 3. Visit 2 Characteristics of the Baseline Population and of Participants Who Did ($n = 5{,}675$) and Did Not ($n = 8{,}345$) Attend Visit 5, Atherosclerosis Risk in Communities Study, 1990–2013

	Attended Visit 2			Attended Visit 5[a]			Did Not Attend Visit 5			*P* Value[b]
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	
Age, years			57.0 (5.7)			54.9 (5.1)			58.4 (5.7)	<0.001
Female sex	7,807	55.6		3,374	59.5		4,433	53.1		<0.001
Race/center										
White										
Washington County, Maryland	3,624	25.9		1,560	27.5		2,064	24.7		<0.001
Minneapolis, Minnesota	3,783	27.0		1,680	29.6		2,103	25.2		<0.001
Forsyth County, North Carolina	3,254	23.2		1,252	22.1		2,002	24.0		0.008
Black										
Forsyth County, North Carolina	372	2.7		93	1.6		279	3.3		<0.001
Jackson, Minnesota	2,987	21.3		1,090	19.2		1,897	22.7		<0.001
Education										
Less than high school	2,983	21.3		715	12.6		2,268	27.2		<0.001
High school	5,852	41.7		2,415	42.6		3,437	41.2		0.107
More than high school	5,185	37.0		2,545	44.9		2,640	31.6		<0.001
Current smoking	3,122	22.3		893	15.7		2,229	26.7		<0.001
Current alcohol use	7,922	56.5		3,483	61.4		4,439	53.2		<0.001
Body mass index[c]			28.0 (5.4)			27.5 (5.0)			28.3 (5.6)	<0.001
Total cholesterol level, mg/dL			210.1 (39.5)			207.3 (37.2)			211.9 (40.9)	<0.001
ApoE genotype (no. of $\varepsilon 4$ alleles)										
0	9,400	69.3		3,951	71.9		5,449	67.5		<0.001
1	3,819	28.1		1,434	26.1		2,385	29.5		<0.001
2	355	2.6		111	2.0		244	3.0		<0.001
Cognitive test score										
Delayed Word Recall Test			6.6 (1.5)			6.9 (1.4)			6.4 (1.6)	<0.001
Digit Symbol Substitution Test			44.6 (14.2)			49.0 (12.9)			41.7 (14.3)	<0.001
Word Fluency Test			33.2 (12.5)			35.7 (11.9)			31.5 (12.6)	<0.001
Global *z* score			0 (1.0)			0.30 (0.9)			−0.21 (1.0)	<0.001
10-year stroke risk score, %			3.1 (4.5)			1.7 (2.1)			4.0 (5.4)	<0.001
Prevalent cardiovascular disease	796	5.8		133	2.4		663	8.1		<0.001
Diabetes mellitus	2,077	14.9		467	8.3		1,610	19.4		<0.001

Abbreviations: ApoE, apolipoprotein E; SD, standard deviation.

[a] Attended visit 5 and completed cognitive testing.

[b] *P* value comparing persons who did and did not attend visit 5.

[c] Weight (kg)/height (m)^2.

possible insensitivity of the tests to changes at the lowest range of their values. The coefficients for the education × time interaction decreased (the apparent advantage for the least educated group was reduced), which is consistent with the likely presence of a floor effect.

DISCUSSION

We found educational level to be largely unrelated to 20-year cognitive change in both black and white participants. Persons with higher education had much better cognitive performance at baseline than those with less education, but performance declined over time in all education strata. With respect to decline, a very small advantage appeared in unweighted analyses for persons with less than a high school education (less decline than among those with more education). The advantage, however, was reduced and became nonsignificant in whites when potential dropout bias was addressed by IPAW or by imputing visit 5 scores for nonexamined persons using the TICS. The advantage was reduced even further by excluding persons with very low scores at baseline, though we caution that such exclusion carries the risk of introducing the adjustment for baseline biases described by Glymour et al. (5). A similar small advantage for the less-than-high-school group was seen among blacks. That advantage was reduced by excluding the persons with

Table 4. Coefficients From GEE Models of Global Cognitive Performance z Score,[a] by Race, Atherosclerosis Risk in Communities Study, 1990–2013

	Unweighted			Weighted (by IPAW) and Stabilized[b]			Imputation With TICS		
	β	SE	*P* for $\beta > \lvert z \rvert$	β	SE	*P* for $\beta > \lvert z \rvert$	β	SE	*P* for $\beta > \lvert z \rvert$
Whites									
Time, years	–0.0101	0.0018	<0.001	–0.0116	0.0020	<0.001	–0.0046	0.0018	0.011
Age, years	–0.0338	0.0015	<0.001	–0.0348	0.0015	<0.001	–0.0331	0.0015	<0.001
Time × age	–0.0019	0.0001	<0.001	–0.0023	0.0002	<0.001	–0.0023	0.0001	<0.001
Time × time	–0.0020	0.0001	<0.001	–0.0020	0.0001	<0.001	–0.0023	0.0001	<0.001
Female sex	0.5205	0.0161	<0.001	0.5194	0.0167	<0.001	0.5237	0.0161	<0.001
Education									
<HS	–1.2160	0.0245	<0.001	–1.2183	0.0252	<0.001	–1.2077	0.0245	<0.001
HS	–0.5218	0.0175	<0.001	–0.5224	0.0182	<0.001	–0.5165	0.0175	<0.001
>HS	0	Referent		0	Referent		0	Referent	
Education × time									
<HS	0.0046	0.0019	0.0145	0.0029	0.0022	0.1838	0.0006	0.0019	0.759
HS	0.0019	0.0012	0.0968	0.0014	0.0014	0.3336	–0.0004	0.0012	0.746
>HS	0	Referent		0	Referent		0	Referent	
Female sex × time	0.0012	0.0011	0.2741	0.0016	0.0014	0.2476	–0.0002	0.0011	0.891
Constant	0.2494	0.0157	<0.001	0.2386	0.0165	<0.001	0.2421	0.0157	<0.001
Blacks									
Time, years	–0.0214	0.0035	<0.0001	–0.0295	0.0038	<0.0001	–0.0201	0.0035	<0.001
Age, years	–0.0377	0.0024	<0.0001	–0.0379	0.0024	<0.0001	–0.0374	0.0024	<0.001
Time × age	–0.0014	0.0002	<0.0001	–0.0015	0.0002	<0.0001	–0.0015	0.0002	<0.001
Time × time	–0.0008	0.0001	<0.0001	–0.0007	0.0002	0.0001	–0.0009	0.0001	<0.001
Female sex	0.3117	0.0275	<0.0001	0.3164	0.0283	<0.0001	0.3114	0.0275	<0.001
Education									
<HS	–1.3013	0.0324	<0.0001	–1.2934	0.0334	<0.0001	–1.3000	0.0325	<0.001
HS	–0.6465	0.0327	<0.0001	–0.6450	0.0335	<0.0001	–0.6443	0.0328	<0.001
>HS	0	Referent		0	Referent		0	Referent	
Education × time									
<HS	0.0085	0.0023	0.0003	0.0079	0.003	0.0047	0.0086	0.0024	0.001
HS	0.0059	0.0023	0.0096	0.0047	0.0028	0.0918	0.0052	0.0023	0.027
>HS	0	Referent		0	Referent		0	Referent	
Female sex × time	0.0018	0.0021	0.3984	0.0041	0.0025	0.0540	0.0018	0.0021	0.399
Constant	0.5481	0.0290	<0.0001	0.5296	0.0299	<0.0001	0.5402	0.0289	<0.001

Abbreviations: GEE, generalized estimating equations; HS, high school; IPAW, inverse probability of attrition weighting; SE, standard error; TICS, Telephone Interview for Cognitive Status.

[a] Results from unweighted GEE, weighted GEE using IPAW stabilized weights, and unweighted GEE using imputation with the TICS are shown. The models included cognitive test data from study visits 2, 4, and 5. Covariates for all 3 models are those listed in the table.

[b] Covariates used to generate IPAW stabilized weights: for the models predicting attrition between visits 2 and 4—hypertension, smoking, global cognitive performance z score, education, age, sex, race/center, diabetes, prevalent coronary heart disease, prevalent stroke, self-reported health, and retirement status; for attrition between visits 4 and 5—1) variables from visit 2 in the previous model; 2) the following variables from visit 4: hypertension, smoking, diabetes, prevalent coronary heart disease, and prevalent stroke; and 3) variables from the most recent annual follow-up telephone call after visit 4 but prior to visit 5—self-reported health; number of recent hospitalizations; physician's diagnosis of stroke, myocardial infarction, or heart failure; hospitalization for stroke, myocardial infarction, or heart failure; functional status; and employment status.

low baseline scores but not by our methods of addressing dropout biases.

The primary effect of education, as we reported earlier (1) and again here, is manifested in much higher cognitive performance levels at baseline: The coefficient for having less than a high school education versus more than a high school education (−1.2 for global z score in whites; −1.3 in blacks) is equivalent to the change estimated for 22 years of additional cognitive aging in a 55-year-old (solving for t with $-1.2 = -0.0101 \times t + -0.0020 \times t^2$). Thus, the cognitive

Table 5. Coefficients From Unweighted GEE Models of Performance on 3 Cognitive Tests,[a] by Race, Atherosclerosis Risk in Communities Study, 1990–2013

	Delayed Word Recall Test			Digit Symbol Substitution Test			Word Fluency Test		
	β	SE	*P* for β > |*z*|	β	SE	*P* for β > |*z*|	β	SE	*P* for β > |*z*|
Whites									
Time, years	0.0103	0.0029	<0.001	−0.0300	0.0015	<0.001	−0.0009	0.0018	0.6078
Age, years	−0.0297	0.0016	<0.001	−0.0429	0.0014	<0.001	−0.0029	0.0016	0.0656
Time × age	−0.0022	0.0002	<0.001	−0.0013	0.0001	<0.001	−0.0009	0.0001	<0.001
Time × time	−0.0032	0.0001	<0.001	−0.0009	0.0001	<0.001	−0.0004	0.0001	<0.001
Female sex	0.4341	0.0175	<0.001	0.5123	0.0160	<0.001	0.2242	0.0175	<0.001
Education									
<HS	−0.4814	0.0267	<0.001	−1.1435	0.0242	<0.001	−1.1025	0.0259	<0.001
HS	−0.1818	0.0190	<0.001	−0.4312	0.0174	<0.001	−0.5569	0.0194	<0.001
>HS	0	Referent		0	Referent		0	Referent	
Education × time									
<HS	−0.0020	0.0030	0.4983	0.0112	0.0014	<0.001	−0.0018	0.0015	0.2222
HS	−0.0018	0.0018	0.3105	0.0041	0.0009	<0.001	0.0008	0.0010	0.4184
>HS	0	Referent		0	Referent		0	Referent	
Female sex × time	0.0059	0.0017	0.0008	−0.0045	0.0009	<0.001	0.0015	0.0010	0.1311
Constant	0.0128	0.0173	0.4591	0.2253	0.0150	<0.001	0.3188	0.0174	<0.001
Blacks									
Time, years	−0.0061	0.0056	0.2748	−0.0234	0.0034	<0.001	−0.0178	0.0034	<0.001
Age, years	−0.0336	0.0029	<0.001	−0.0409	0.0023	<0.001	−0.0138	0.0025	<0.001
Time × age	−0.0017	0.0003	<0.001	−0.0007	0.0001	<0.001	−0.0010	0.0002	<0.001
Time × time	−0.0019	0.0002	<0.001	−0.0003	0.0001	0.0338	0.0000	0.0001	0.9889
Female sex	0.3139	0.0329	<0.001	0.3261	0.0265	<0.001	0.1030	0.0300	0.0006
Education									
<HS	−0.4949	0.0380	<0.001	−1.2706	0.0316	<0.001	−1.3170	0.0345	<0.001
HS	−0.1888	0.0377	<0.001	−0.6174	0.0345	<0.001	−0.7308	0.0368	<0.001
>HS	0	Referent		0	Referent		0	Referent	
Education × time									
<HS	−0.0024	0.0037	0.5141	0.0109	0.0018	<0.001	0.0089	0.0019	<0.001
HS	0.0017	0.0036	0.6223	0.0054	0.0018	0.0029	0.0073	0.0021	<0.001
>HS	0	Referent		0	Referent		0	Referent	
Female sex × time	0.0038	0.0032	0.2356	−0.0018	0.0016	0.2526	0.0028	0.0018	0.1354
Constant	0.1002	0.0336	0.0027	0.5234	0.0291	<0.001	0.6721	0.0335	<0.001

Abbreviations: GEE, generalized estimating equations; HS, high school; SE, standard error.

[a] Cognitive test data from study visits 2, 4, and 5.

status of a 55-year-old with more than a high school education is estimated to decline to the baseline level of the person with less than a high school education only after 22 years. However, since cognitive decline occurs at a similar (or slightly slower) rate in the less educated, those large baseline differences persist or are reduced only slightly—by magnitudes so small that they are hardly appreciable in Figure 2. Since the differences generally lose statistical significance or are inconsistent in our models accounting for attrition or floor effects, we believe that our results support a lack of clinically meaningful associations between education and cognitive change *in either direction*, when individuals are evaluated over 20 years and across several cognitive domains.

We found variable results for individual cognitive tests. The Digit Symbol Substitution Test, like the global *z* score but unlike the Delayed Word Recall Test and the Word Fluency Test, showed that decline was somewhat steeper in persons with higher educational levels. This may be because the skills required for the Digit Symbol Substitution Test, a test of psychomotor speed, memory, and executive function, are gained with more years of education and other continuing experience, including possibly employment. Such skills may be the first to deteriorate with age. As Glymour et al.

Table 6. Coefficients From Unweighted GEE Models of Global Cognitive Performance *z* Score,[a] by Race, Excluding Persons With a Visit 2 Global *z* Score Less Than the Fifth Percentile, Atherosclerosis Risk in Communities Study, 1990–2013[b]

	Whites			Blacks		
	β	SE	*P* for β > |*z*|	β	SE	*P* for β > |*z*|
Time, years	−0.0140	0.0018	<0.001	−0.0242	0.0035	<0.001
Age, years	−0.0297	0.0014	<0.001	−0.0321	0.0022	<0.001
Time × age	−0.0020	0.0001	<0.001	−0.0015	0.0002	<0.001
Time × time	−0.0018	0.0001	<0.001	−0.0007	0.0001	<0.001
Female sex	0.4534	0.0152	<0.001	0.2717	0.0262	<0.001
Education						
<HS	−1.0090	0.0223	<0.001	−1.1578	0.0307	<0.001
HS	−0.4820	0.0167	<0.001	−0.6323	0.0321	<0.001
>HS	0	Referent		0	Referent	
Education × time						
<HS	0.0015	0.0020	0.443	0.0060	0.0024	0.010
HS	0.0012	0.0012	0.323	0.0057	0.0023	0.013
>HS	0	Referent		0	Referent	
Female sex × time	0.0025	0.0011	0.023	0.0025	0.0021	0.230
Constant	0.3051	0.0150	<0.001	0.5729	0.0283	<0.001

Abbreviations: GEE, generalized estimating equations; HS, high school; SE, standard error.

[a] Cognitive test data from study visits 2, 4, and 5.

[b] The analysis used race-specific cutpoints ($z < -1.678$ for whites; $z < -1.66747$ for blacks).

hypothesized elsewhere, “education might predict accelerated cognitive decline under a ‘last in, first out’ model” (25, p. 751), specifically proposing that tests of verbal fluency and verbal memory employ the prefrontal cortex, which might be particularly vulnerable in persons with neurodegenerative and cerebrovascular disease (25). The apparently greater decline in the most educated group might also reflect regression to the mean.

Our findings pertain to the utility of evaluating cognitive change in relation to vascular or other risk factors, because potentially confounding factors such as education are associated cross-sectionally with cognitive performance but not with *change* in cognitive performance. Numerous studies suggest increased risk of dementia among persons with less education (6). This supports a concept of “cognitive reserve”—specifically that education may increase neural networks or alternative synaptic pathways, allowing individuals to compensate better for concomitant neurodegeneration resulting from aging or specific brain diseases, or even somehow preventing further neurodegeneration (26). Our lack of an association between education and cognitive change suggests, as we proposed before (1), that the often-reported association of higher education with lower dementia incidence may simply be due to education’s raising an individual’s baseline cognitive performance so much that the time needed to decline to the threshold of a dementia diagnosis is increased. In proposed models of Alzheimer’s disease pathogenesis, cognitive reserve is hypothesized to delay the clinical appearance of overt cognitive impairment but not to impact the actual neurodegenerative processes leading to Alzheimer’s disease (27).

Although earlier studies suggested that education may protect against cognitive decline (11, 13), these studies were often limited by biases inherent in the analytic approach, as described by Glymour et al. (5). Recent studies conducted with more appropriate analytic techniques have generally not shown education to be protective against cognitive change. Some of these studies either used global tests such as the MMSE, which is insensitive to small changes in high-functioning individuals (7), or were limited to a single or global cognitive domain (10). In addition, studies (including our own (1)) that have a shorter duration of follow-up (9) or include only people of younger ages (12) may not evaluate the most critical time period during which most cognitive decline occurs. Our study also evaluated a biracial population, of both men and women, who were first tested in middle age. Additionally, many previous studies failed to take selective dropout into account. Analyzing data from only those persons who are present at a study visit, when the likelihood of coming to a visit is associated with cognitive and educational status, may be deceptive. By including 2 different methods (TICS imputation and IPAW) of accounting for this dropout, we were able to evaluate how results might change after appropriately accounting for this dropout. With our analyses, we have confirmed that even after accounting for dropout, poor education is not associated with greater cognitive decline.

Our study had limitations. If the assumptions of ignorability or positivity were violated or if our IPAW model were misspecified, the model would be inadequate, and the cognitive decline in poorly educated persons would probably be underestimated. However, we did not find evidence of structural positivity violations. Moreover, we evaluated more comprehensive IPAW models without appreciable changes in results. The models we used employed data from recent phone calls proximal to dates of attrition and were highly predictive of censoring and death. It is also possible that cases of dementia might be missed (persons with dementia were less likely to attend visit 5); future studies can analyze the role of scoring options for these missing individuals.

The shape of the cognitive trajectory could be defined better with more testing occasions, but our unweighted models using 5 testing occasions did not change any of the conclusions drawn from the models using 3 testing occasions. The TICS imputation was also limited by the long time interval between visit 4 and the TICS assessment and the small number of nonexamined individuals with the TICS assessment, leading to limited precision in estimating associations.

In summary, our data show that among persons with repeat cognitive evaluations over 20 years and into older age, educational attainment was strongly associated with cognitive performance at baseline but not with cognitive decline. Methods used to account for selective dropout did not alter these conclusions. Further studies to understand reasons for the often-observed association of higher education, or perhaps related social occupational or other cultural factors, with reduced dementia incidence are needed.

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Appendix Table 1. Mean Scores on the Delayed Word Recall Test, Digit Symbol Substitution Test, and Word Fluency Test From Study Visits 2 and 3,[a] by Race and Education, Atherosclerosis Risk in Communities Study, 1990–1995

Cognitive Test and Study Visit	Whites			Blacks		
	<HS	HS	>HS	<HS	HS	>HS
Delayed Word Recall Test						
Visit 2	6.13	6.66	6.96	5.81	6.22	6.54
Visit 3	6.25	6.70	7.00	5.66	6.28	6.36
Digit Symbol Substitution Test						
Visit 2	36.93	45.18	49.77	23.74	31.48	39.39
Visit 3	36.28	45.54	50.71	21.94	30.07	37.09
Word Fluency Test						
Visit 2	26.68	31.86	38.33	20.77	28.81	38.38
Visit 3	26.29	31.98	38.52	20.11	27.75	37.37

Abbreviation: HS, high school.

[a] Evaluation of possible practice effects.