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Research Article

Education and Cardiovascular Health as Effect Modifiers of APOE ε4 on Dementia: The Atherosclerosis Risk in Communities Study

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Abstract

Background: Both education and cardiovascular risk factors are strongly associated with dementia risk. However, it is not clear whether these associations persist or vary among individuals with high genetic risk for Alzheimer's disease. We examined the interactive relationship between lifestyle and genetic dementia risk factors in a prospective cohort study.

Methods: Our data came from the Atherosclerosis Risk in Communities study participants (n = 13 715; baseline age 45–64; 25% Black; 55% female), who were followed for incident dementia from 1987 through 2017. We used Cox proportional hazard models to estimate the risk of dementia (ascertained through in-person examination, telephone cognitive screeners, and/or hospital and death records) associated with baseline education and cardiovascular risk factors (measured using the American Heart Association's "Life Simple 7") among ε4 carriers and non-carriers separately. We also examined differences by race and sex.

Results: Two thousand two hundred and twenty-six incident dementia cases occurred over a median 25 years of follow-up. Lower educational attainment and poorer cardiovascular health were associated with greater risk of incident dementia. There was an education by apolipoprotein E (APOE) status interaction (p = .005) whereby the association of education and dementia was weaker for ε4 carriers (HR college graduates vs less than high school: 0.71 [0.59–0.84] than non-carriers (0.54 [0.47–0.63]). There was no interaction between APOE status and cardiovascular health on dementia risk. These relationships did not vary significantly by race or sex.

Conclusions: Education and cardiovascular health were associated with lower dementia risk regardless of APOE genotype, though the protective effects of education were somewhat diminished among ε4 carriers.

Keywords: Cognitive aging, Gene by environment, Life Simple 7

The apolipoprotein E (APOE) ε4 allele is a significant genetic risk factor for Alzheimer's disease and dementia (1–3). However, this relationship is not deterministic. Many APOE ε4 carriers live to old age without developing dementia, and nongenetic factors can alter how this allele is expressed (4). Risk of dementia is delayed or mitigated among people with higher education and good cardiovascular

health (5,6). However, it is unclear whether APOE modifies educational and cardiovascular health gradients in dementia risk. In this study, we ask: Does APOE ε4 *magnify* or *diminish* the influence of education and midlife cardiovascular health factors (which are also associated with APOE genotype (7)) on future risk of dementia?

Previous research investigating whether educational and cardiovascular health gradients in dementia risk are modified by APOE genotype have yielded mixed results (8–19). Many of the prior studies addressing this question had poor precision to identify statistically significant interactions or perform sub-group analyses by key characteristics such as sex and race. Sub-group analyses are important because the association between APOE and dementia has been shown to be weaker for women compared with men at young ages and weaker for African Americans compared with White Americans (20,21). Previous studies also tend to have a limited follow-up time (10 years or less), which allows them to only consider how cardiovascular factors in late-life influence dementia risk. Late-life cardiovascular factors tend to have weaker associations with dementia risk than those measured in midlife (22).

Theoretical models suggest 2 competing hypotheses for gene–environment interactions (23). According to the diathesis-stress model, environmental gradients in dementia risk would be attenuated among those with low genetic risk for the disease, because poor social environments may "trigger" genetic predisposition for dementia. By contrast, the "social push" model posits that genetic differences in disease risk are more influential in positive social environments where genetic predisposition has an opportunity to "shine through." According to the social push model, environmental gradients in disease risk would be smaller among those with high genetic risk for dementia.

From a public health and policy perspective, it would be valuable to show that modifiable factors—such as higher education and improved cardiovascular health factors—are associated with lower risk of dementia even among individuals who have elevated genetic risk. This study will examine education and cardiovascular health as potential modifiers by (a) describing the education and cardiovascular health gradient in dementia risk within categories of APOE genotype, (b) testing for a gene–environment interaction effect to explore whether APOE ε4 magnifies or diminishes the associations of these risk factors on dementia risk, and (c) exploring whether this effect modification differs by sex or race.

Method

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based prospective cohort study of 15 792 mostly Black and White American men and women from 4 regions: suburbs of Minneapolis, MN; Washington County, MD; Forsyth County, NC; and Jackson, MS. The institutional review boards at each participating institution approved study protocols and all participants provided written informed consent at each visit. ARIC participants were 45–64 years old at study baseline (1987–1989). The current analysis uses data through visit 6 (2016–2017). Participants who were neither White nor Black were excluded (n = 48), as were Black participants in Minnesota and Maryland (n = 55), due to small numbers for the race-stratified analysis. We also excluded one participant with prevalent dementia at baseline, and 1 973 participants due to missing data on education (n = 27), cardiovascular health (n = 1 336), APOE (n = 683), or who did not consent for genetic research (n = 120). These restrictions yielded a final analytic sample of 13 715.

Assessment of APOE, Education, and Cardiovascular Health

DNA was extracted from blood specimens collected at ARIC visits 2 or 3. As has been described previously (24), APOE genotypes were determined using the TaqMan assay (Applied Biosystems, Foster City, CA) to identify polymorphisms at codons 112 and 158 separately. Data from each codon were combined to identify participants' full genotype. The 6 possible combinations of APOE alleles were reduced to a binary indicator of any ε4 versus none.

Participants self-reported the highest grade they had completed at the first visit. We reduced the various levels of education to 3 categories: those with 0–11 years of education, high school graduates and those with vocational training, and those with any years of college education.

Cardiovascular health scores were created using the American Heart Association's (AHA) "Life's Simple 7" (LS7) guidelines. The LS7 consists of 7 risk factors and behaviors that impact cardiovascular health: blood pressure, total cholesterol, serum glucose, physical activity, diet, body mass index (BMI), and smoking (25). Each component was measured during the baseline examination in ARIC. Trained technicians measured blood pressure 3 times using a random-zero sphygmomanometer, and the mean of the last 2 measurements was used. Fasting blood drawn from ARIC participants was analyzed to measure total cholesterol and serum glucose. Physical activity was determined using the Baecke questionnaire (26), which asked participants to report how frequently they participated in sports and walking in the previous year; these measures were converted to minutes per week of moderate and vigorous exercise. Diet was assessed using a food frequency questionnaire. The AHA defines 5 ideal components of a healthy diet: ≥4.5 servings/d of fruits and vegetables, ≥2 3- to 5-oz servings/wk of fish, ≥3 servings/d of whole grains, <1 500 mg/d of sodium, and ≤4 glasses/wk of sugar sweetened beverages (25). BMI was calculated from measured height and weight. Participants self-reported smoking status and brought pill bottles of medications and supplements taken in the last 2 weeks to the visit. Medication names and dosages were recorded, and later classified according to treatment objective (eg, antihypertensive, cholesterol lowering, glucose lowering). For each LS7 component, participants receive a score of 0, 1, or 2 based on whether they meet poor, intermediate, or ideal standards, respectively, according to the AHA. These standards, shown in Supplementary Table S1, were modified slightly to fit the ARIC data, as has been done previously (27). Scores for all 7 components are summed to a single variable, ranging from 0 to 14, to measure total cardiovascular health. We then classified participants as having poor (0–4), intermediate (5–9), or ideal (10–14) cardiovascular health.

Incident Dementia

Several different approaches were used to ascertain incident dementia during follow-up (28). First, ARIC participants attending visit 5 (2011–202013) and 6 (2015–2017) underwent a detailed neurocognitive assessment, and a selected subset received a neurological exam and brain magnetic resonance imaging. Second, the modified telephone interview for cognitive status (TICSm) was performed in participants who at the time of visit 5 were alive but unable or unwilling to participate in an in-person exam. Informants provided additional information in some instances, when participants were

deceased or unable to complete the TICSm assessment themselves. Third, since 2012 the Six Item Screener (SIS) has been administered twice-yearly during surveillance phone calls and has been followed with an informant AD8 Dementia Screening Interview (AD8) when appropriate. Lastly, dementia diagnosis was determined via hospital discharge codes and diagnostic codes from death certificates. A validation study within ARIC-NCS comparing clinic-based cognitive assessment at visit 5 to hospital diagnostic codes reported that the specificity of hospital diagnostic codes for dementia was 99% (95% CI: 99%–99%), but the sensitivity was 25% (95% CI: 22%–29%) (28). So, dementia cases diagnosed by medical or death records are likely to be true cases; however, many cases will be missed. However, after 2012, ARIC's twice-yearly dementia screening using the SIS and AD8 should have captured many cases that did not have hospitalization ICD codes. Among dementia cases included in the present analysis, approximately 30% of dementia cases were identified using hospital and death records alone; the remaining 70% were adjudicated during an in-person examination and/or phone screener. Due to low sensitivity among dementia cases identified through hospital and death records alone, we conducted sensitivity analyses that excluded these cases.

Incident dementia was defined according to the methodology previously used in ARIC, using data from all of the potential diagnostic sources described above (ie, clinic visit assessment, TICSm, SIS/AD8, and hospital discharge and death codes), with adjudication by an expert panel (28). A flow chart of the ARIC study is provided in the **Supplementary Material** showing dates, sample sizes, and methods of ascertaining dementia diagnosis at each visit (**Supplementary Figure 1**).

Statistical Analysis

The date of the first ARIC examination served as the beginning of the observation period. Follow-up time extended until the first dementia diagnosis, death, loss to follow up, or the end of visit 6 (December 31, 2017). If the diagnosis was derived from a hospital discharge or death code, 6 months were subtracted from this date to approximate the date of onset. Poisson regression was used to calculate incidence rates. We used multivariable Cox proportional hazard models to estimate the effects of education and cardiovascular health on dementia risk. For the primary analyses, first we estimated the adjusted main effects of education, cardiovascular health, and APOE genotype on dementia risk in the full ARIC sample. Next, we used cross-product terms to assess the multiplicative interaction between education and APOE genotype and between cardiovascular health and APOE genotype separately. Regardless of whether an interaction was present, we estimated models separately among ε4 carriers and non-carriers. We also conducted subgroup analyses by race (Black or White) and sex. To adjust for potential confounding, all models adjust for baseline age, sex, race, and field site. Because 3 of the field sites had participants of only a single race, some models combine race and field site into a 5-category variable (White-Minnesota, White-Maryland, Black-Mississippi, White-North Carolina, Black-North Carolina). We confirmed the proportional hazards assumption graphically by comparing the ln(-ln) survival curves for the education and cardiovascular health groups. Analyses were conducted in Stata 14 (StataCorp LLC, College Station, TX).

As a sensitivity check, we replicated our analyses in the full sample after excluding incident dementia cases ascertained through hospital or death records alone(so, all dementia events were identified via in-person clinic assessments or phone SIS and AD8 screening). We did not conduct race- and sex-stratified analyses on this restricted sample due to smaller sub-group sample sizes.

Results

Characteristics of Sample

Of the 13 715 participants in our analysis, approximately 55% (n = 7 574) were female and 25% (n = 3 406) were Black. The mean age at baseline was 54.2 ± 5.8 years. Twenty-three percent (n = 3 145) did not complete high school, 41% (n = 5 652) had a high school diploma or vocational training, and 36% (n = 4 918) had some college education.

Based on our categorization of LS7, 8% (n = 1 043) had poor cardiovascular health, 65% (n = 8 907) had intermediate cardiovascular health, and 27% (n = 3 765) had ideal cardiovascular health. The prevalence of the composite LS7 score, and each LS7 risk factor, varied significantly by sex and race. However, across race and sex groups, there was broad similarity in which factors contribute most to the LS7 composite score (Supplementary Table S2).

Sixty-nine percent (n = 9 524) of the sample did not carry an APOE ε4 allele, while 31% (n = 4 191) did. Approximately 3% of the sample (N = 359) had 2 copies of the ε4 allele; however, because of the small sample size, we did not analyze this group separately. The distribution of APOE allele frequency in ARIC matched other population-based samples of midlife adults (29). There were several significant differences between APOE ε4 carriers and non-carriers. Black participants were more likely to be APOE ε4 carriers. APOE ε4 carriers were also more likely to have basic education and have poor or intermediate cardiovascular health, although the magnitude of the educational and cardiovascular health differences by APOE genotype were small (**Table 1**).

Dementia Risk Analysis in Full Sample

The median follow-up time in the sample was 25 years. Over follow-up, 2 226 cases of incident dementia were observed. As expected, the percentage of individuals who were diagnosed with dementia was higher among ε4 carriers than non-carriers (23.1% and 13.2%, respectively).

We estimated the main effects of education, cardiovascular health, and APOE genotype on dementia risk in the full sample in separate models adjusting for baseline age, race, and sex. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI) in (**Table 2**). In the model that adjusted only for demographic variables, age was a significant predictor of dementia risk (HR: 4.64, CI: 4.28–5.03 for a 10-year age difference at baseline). Blacks had a higher dementia risk than Whites (HR: 1.86, CI: 1.70–2.04) and men had modestly higher risk than women (HR: 1.09, CI: 1.00–1.19). Dementia risk was lower among high school graduates (HR: 0.70, CI: 0.63–0.78) and those with college education (HR: 0.59, CI: 0.53–0.66) compared to those who did not complete high school. In direct comparisons where high school graduates were the reference, participants with a college education were at significantly lower risk of dementia (HR: 0.85, CI: 0.76–0.94), signifying additional benefits of college over high school education.

Cardiovascular health was also associated with risk of dementia. Compared to those with a poor cardiovascular health score, those with intermediate health (HR: 0.61, CI: 0.52–0.71) and those with ideal health (HR: 0.45, CI: 0.37–0.53) had significantly lower risk of dementia. In direct comparisons where intermediate cardiovascular health score was the reference, participants with ideal health were at significantly lower risk of dementia (HR: 0.73, CI: 0.66–0.81), indicating additional benefits of ideal over intermediate cardiovascular health. APOE ε4 carriers had greater risk of dementia than non-carriers (HR: 1.97, CI: 1.81–2.14).

Table 1. Baseline Characteristics of Study Participants by APOE ε4 Status (*N* = 13 715): The Atherosclerosis Risk in Communities Study (1987–1989)

Characteristic	APOE ε4 Non-carrier	APOE ε4 Carrier	*p* Value*
N	9 524	4 191	
Baseline, *N* (%)†			
Age, mean ± *SD*	54.2 ± 5.7	54.3 ± 5.8	.28
Black	2 044 (21.46)	1 362 (32.50)	<.001
Female	5 286 (55.50)	2 288 (54.59)	.32
Education level			.009
<High school	2 119 (22.25)	1 026 (24.48)	
High school/ vocational	3 985 (41.84)	1 667 (39.78)	
College	3 420 (35.91)	1 498 (35.74)	
Total Cardiovascular Health‡			<.001
Poor	672 (7.06)	371 (8.85)	
Intermediate	6 134 (64.41)	2 773 (66.17)	
Ideal	2 718 (28.54)	1 047 (24.98)	
Incident dementia	1 265 (13.19)	970 (23.14)	<.001

Notes: APOE = apolipoprotein E.

**p*-value calculated from *t*-test (for age) or chi-squared test (for categorical variables).

†N (%) of participants unless indicated otherwise.

‡Cardiovascular health defined as poor (0–4), intermediate (5–9), or ideal (10–14) based on AHA guidelines for ideal cardiovascular health.

Education and Dementia Risk Analysis Stratified by APOE Genotype

We first calculated the age-adjusted incidence rates of dementia by education and APOE genotype using Poisson regression. These rates are displayed in Panel A of Figure 1. Rates among ε4 carriers were significantly higher than non-carriers at every education level, though an educational gradient in dementia incidence was apparent in both groups. Among ε4 carriers incidence rates (per 1 000 person years) were 13.31 (CI: 11.79–14.83) for those who did not complete high school, 10.64 (CI: 9.54–11.74) for high school graduates, and 10.13 (CI: 9.01–11.26) for those with a college degree. Whereas among ε4 non-carriers, the incidence rates were 8.59 (CI: 7.75–9.43), 5.90 (CI: 5.38–6.42), and 4.92 (CI: 4.40–5.44) for those who did not complete high school, high school graduates, and college-educated participants, respectively.

We estimated the relative effect of education on dementia in multivariable Cox models and found that the association differed by APOE ε4 status (p = .005 for interaction). Compared to those who did not complete high school, those who graduated high school had a lower risk of dementia whether they were ε4 non-carriers (HR: 0.68 [CI: 0.59–0.79]) or ε4 carriers (HR: 0.77 [CI: 0.65–0.91]). The HR for college graduates compared to those without a high school diploma was 0.54 (CI: 0.47–0.63) among ε4 non-carriers and 0.71 (CI: 0.59–0.84) among ε4 carriers. These estimates were substantively similar in a sensitivity check after excluding incident dementia cases identified via hospital discharge or death records alone (Supplementary Table S3).

We compared the effects of education on dementia by APOE genotype within sex and race groups (**Table 3**). Among women, the APOE × education interaction term was statistically significant (p = .030). The results for women closely matched the results for the full sample; the magnitude of the effect was greater for college-educated women compared with those who did not complete high school among ε4 non-carriers (HR: 0.51, CI: 0.41–0.62) than among ε4 carriers (HR: 0.70, CI: 0.56–0.88). APOE × education interaction terms were not statistically significant for men or for either race group. However, within each race, sex, and APOE group, higher educational attainment was associated with significantly lower dementia risk.

Cardiovascular Health and Dementia Risk Analysis Stratified by APOE Genotype

The age-adjusted incidence rates (per 1 000 person years) of dementia by cardiovascular health and APOE genotype indicated that for both ε4 carriers and non-carriers, better cardiovascular health was associated with lower dementia risk (**Figure 1B**). Among ε4 non-carriers, the incidence rates were 7.22 (CI: 5.72–8.72), 6.56 (CI: 6.12–7.00), and 5.13 (CI: 4.55–5.72) among those with poor, intermediate, and ideal health, respectively. Rates were higher among ε4 carriers: 14.21 (CI: 11.32–17.10) for poor health, 11.40 (CI: 10.53–12.27) for intermediate health, and 9.63 (CI: 8.33–10.93) for ideal health.

Interaction of cardiovascular health and APOE genotype on dementia risk were further analyzed in Cox models (**Table 4**). In the full sample, we observe that cardiovascular health reduced dementia risk for both APOE ε4 carriers and non-carriers, as indicated by nonsignificant interaction by APOE ε4 carrier status (p = .48). Compared to those with poor health, ε4 non-carriers with intermediate health had a lower risk of dementia (HR: 0.69 [CI: 0.55–0.86]) as did ε4 carriers (HR: 0.64 [CI: 0.52–0.81]). The HR for those with ideal health was 0.53 (CI: 0.42–0.68) among ε4 non-carriers and 0.51 (CI: 0.39–0.66) among ε4 carriers. These estimates were substantively similar in a sensitivity check after excluding incident dementia cases identified via hospital discharge or death records alone (Supplementary Table S4).

We explored the joint effects of cardiovascular health and APOE genotype on dementia risk within sex and race groups. Among women, the APOE × cardiovascular health interaction term was significant (p = .011), indicating a stronger association between cardiovascular health and risk of dementia for ε4 non-carriers. No significant APOE × cardiovascular health interactions were observed within the other subgroups. For all groups, the pattern persisted whereby better cardiovascular health was associated with lower dementia risk. However, at times precision in stratified models was low and estimates were not statistically significant.

Discussion

This study evaluated the joint effects of education, cardiovascular health, and APOE genotype on incident dementia in a sample of 13 715 Black and White men and women from 4 communities in the United States who were followed for a median of 25 years. Our results provide novel evidence that the known education (30) and cardiovascular health (22,31) gradients in dementia risk persist among both ε4 carriers and non-carriers. This indicates that even individuals with high genetic risk for dementia may benefit from improving these modifiable risk factors for the disease, and that societal initiatives to expand and enhance education among youth may have added benefits of reducing dementia risk in later life.

In the present analysis, although higher education is associated with lower dementia risk regardless of APOE status, the effect is modestly stronger among ε4 non-carriers. This suggests that people

Table 2. Main Effect Adjusted HR and 95% CIs for Risk of Incident Dementia: The Atherosclerosis Risk in Communities Study (1987–2017)

N total	**13 715**			
N incident dementia	**2 226**			
	Main effect models* (HR [95% CI])			
	Model 1	Model 2	Model 3	Model 4
	Demographics	Demographics and Education	Demographics and Cardiovascular Health	Demographics and APOE ε4 carrier status
Age, per 10 years	4.64 (4.28, 5.03)	4.37 (4.03, 4.74)	4.53 (4.17, 4.91)	4.67 (4.31, 5.06)
Race				
White	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Black	1.86 (1.70, 2.04)	1.68 (1.53, 1.85)	1.66 (1.51, 1.82)	1.70 (1.55, 1.86)
Sex				
Female	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Male	1.09 (1.00, 1.19)	1.09 (1.01, 1.19)	1.10 (1.01, 1.20)	1.06 (0.98, 1.16)
Education				
<High school		1 (Ref)		
High school		0.70 (0.63, 0.78)		
College		0.59 (0.53, 0.66)		
Cardiovascular health†				
Poor			1 (Ref)	
Intermediate			0.61 (0.52, 0.71)	
Ideal			0.45 (0.37, 0.53)	
APOE genotype				
ε4 non-carrier				1 (Ref)
ε4 carrier				1.97 (1.81, 2.14)

Notes: APOE = apolipoprotein E; CI = confidence interval; HR = hazard ratio.

*Estimates from all variables included in the main effect models are provided.

†Cardiovascular health defined as poor (0–4), intermediate (5–9), or ideal (10–14) based on AHA guidelines for ideal cardiovascular health.

with higher genetic risk for dementia benefit somewhat less from advanced educational attainment than lower-risk individuals do. The cognitive reserve theory suggests that education and participation in cognitively stimulating activities protects against dementia by increasing the brain's ability to compensate for damage caused by Alzheimer's disease and related dementia pathologies (32–34). APOE ε4 inhibits synaptic regeneration, thus making it more difficult for the brain to cope with neuronal loss (35). Individuals with low educational attainment and APOE ε4 would thus be most vulnerable to dementia. In our analysis, main effects for both education and APOE ε4 were as expected, however advanced education was less protective among ε4 carriers that among non-carriers. One possible explanation for this finding is that the adverse effects of APOE ε4 mitigated some of the benefits of education among ε4 carriers.

This effect modification (ie, diminished effect of education on dementia risk among ε4 carriers) was statistically significant in the full sample and among women. Although the interaction was nonsignificant among men or within either race group, the pattern was consistent across all groups, whereby magnitudes of effect for the association between education and incident dementia were weaker among ε4 carriers than non-carriers.

Prior research evaluating this association has yielded conflicting results, with some studies finding opposite conclusions regarding an APOE × education interaction (9–11). In an analysis of data from the MacArthur Study of Successful Aging, researchers found that among 865 U.S. adults aged 70–79 years at baseline, among individuals carrying an APOE ε4 allele the protective effect of education on dementia risk was diminished (8). A study of 932 adults from Sweden aged 75 years and older at baseline showed opposite results: the education gradient in dementia risk was magnified among APOE ε4 carriers compared with non-carriers (9). By contrast, no interaction effect was observed in 2 other studies of Scandinavian participants aged 65 years and older where the education gradient in dementia risk was observed across APOE genotype groups, but genetic risk did not alter the magnitude of this gradient (10,11).

However, precision was poor for these previous studies which included between 895 and 1 389 individuals, and between 61 and 324 cases of incident dementia. By contrast, our study had high precision with a sample size of 13 715 and 2 226 incident dementia cases. Our study concurs with the finding that educational gradients are diminished among APOE ε4 carriers.

The divergence of results across these studies may be partially a function differences in study population and measurement. Interestingly, we find similar results to the MacArthur Study (8), which was also used data from the United States. The studies with contradictory results were based in Sweden and Finland, which have far lower social stratification than the United States (36). It is possible that differences in national policy environment influence educational gradients in dementia risk. Furthermore, these studies differed with respect to the measurement of education level. Our study and the MacArthur Study (8) used college as the top level of education, while the 3 Scandinavian studies used 8 or 9 years of schooling as the upper cutoff (9–11). If the interaction between education and APOE primarily occurs at the tertiary level, these studies would not have been able to observe this result.

In the ARIC data, better cardiovascular health was associated with lower dementia risk, regardless of APOE status. This pattern was present in the full sample and within sex and race sub-groups.

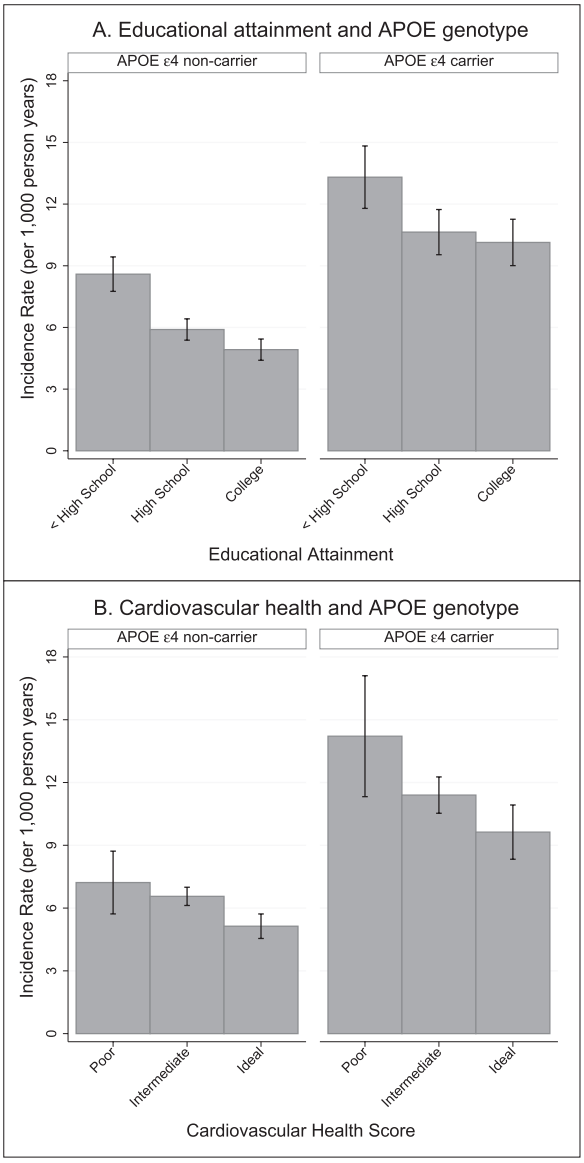

Figure 1. Age-adjusted incidence rates of dementia by educational attainment, cardiovascular health, and APOE genotype, Atherosclerosis Risk in Communities Study, 1987–2017. Note: Incidence rates estimated from Poisson regression models with adjustment for age. Error bars show 95% confidence intervals. Models in Panel A adjusted for education and APOE main and interactive effects. Models in Panel B adjusted for cardiovascular health score and APOE main and interactive effects. Cardiovascular health defined as poor (0–4), intermediate (5–9), or ideal (10–14) based on AHA guidelines for ideal cardiovascular health.

Among women, there was an interaction, whereby the association between cardiovascular health and dementia risk was stronger among ε4 non-carriers. The pattern of cardiovascular risk factors contributing to the composite score was similar in men and women (Supplementary Table S2). Therefore, we do not believe that this interaction is driven by sex difference in risk factor patterns. A previous analysis of nearly 58 000 research subjects in the Global Alzheimer's Association Interactive Network reported that APOE ε4 had a stronger effect on dementia risk for women than men, especially at younger ages (20). Additional research is needed to elucidate mechanisms underlying sex and racial differences in the association between APOE ε4 and dementia risk, and to replicate our findings of an interaction between ε4 status and cardiovascular health on dementia incidence.

Previous research regarding cardiovascular risk factors, APOE, and dementia risk have generated contradictory results (12–19). An observational study of 1 646 Canadians aged 65 and older at baseline found that exercise significantly reduced risk of dementia among APOE ε4 non-carriers, but it had no effect among ε4 carriers (12). This same interaction effect between physical activity, APOE genotype, and dementia was observed in an analysis of the Cardiovascular Health study which included 3 375 Americans aged 65 years and older at baseline (13). An additional study of 1 987 Americans aged 65 years and older in the Washington Heights-Inwood Columbia Aging Project found that optimal cardiovascular health was protective against dementia for APOE ε4 non-carriers only (14). Contradicting these results, a study of 1 284 individuals from Finland, of whom 61 developed incident dementia, showed that the relationship between midlife lifestyle risks (including diet, physical activity, alcohol consumption, and smoking) and late-life (mean age 71) dementia was stronger among APOE ε4 carriers compared with non-carriers (15). Several other prospective aging studies have shown that cardiovascular and genetic risks for dementia operate independently of each other (16–19).

However, most of these studies suffered from relatively small sample sizes and short follow-up, thus limiting the number of dementia events they could observe and their statistical power to detect significant effects. In the present analyses, we observed 2 226 dementia cases over follow-up, and so had greater power to detect interaction effects. Some of these differences between studies may also be related to the timing of cardiovascular risk measurement. Late-life cardiovascular factors tend to have weaker associations with dementia risk than those measured in midlife (22). We relied on midlife measurement in the present study.

Our findings have important implications for public health and clinical practice in the age of precision medicine. Encouragingly, we find that that the educational and cardiovascular health gradients in dementia incidence persist even for APOE ε4 carriers. This suggests that individuals who have high genetic risk for dementia can still mitigate their risk level by modifying their lifestyles. However, we also find that the effect of education on dementia risk is weaker among APOE ε4 carriers than non-carriers.

Strengths and Limitations

This study contributes to existing literature on the joint effects of education, cardiovascular health, and APOE on dementia risk in several important ways. First, our sample contains over 9 000 APOE ε4 non-carriers and over 4 000 ε4 carriers. This large sample gave us enough statistical power to detect even a modest interaction effect, and to look at whether effect estimates where consistent by sex and race. Previous studies have been limited by only having several hundred cases of each APOE genotype, thus rendering null results inconclusive. Our study also benefited from a long follow-up period of 25 years at median. Many prospective studies of dementia only have follow-up periods of 10 years or less. This allows us to estimate the effects of midlife cardiovascular health on late-life dementia, which is important since dementia has a long natural history and associations between vascular health and dementia incidence are often stronger when risk factors are measured in midlife compared to late life (22,30,31).

Table 3. Adjusted HR and 95% CIs of Dementia Associated with Educational Attainment Stratified by APOE Genotype Carrier Status, Race, and Sex: The Atherosclerosis Risk in Communities Study (1987–2017)

	APOE ε4 Non-carriers		APOE ε4 Carriers		APOE × Edu *p*-value
	$N_{dementia}/N_{total}$	HR (95% CI)	$N_{dementia}/N_{total}$	HR (95% CI)	
Full Sample					
Education					.005
< High school	405/2 119	1 (Ref)	296/1 026	1 (Ref)	
High school	500/3 985	0.68 (0.59, 0.79)	362/1 667	0.77 (0.65, 0.91)	
College	351/3 420	0.54 (0.47, 0.63)	312/1 498	0.71 (0.59, 0.84)	
Women					
Education					.030
< High school	246/1 181	1 (Ref)	169/537	1 (Ref)	
High school	316/2 423	0.64 (0.54, 0.76)	222/999	0.69 (0.55, 0.85)	
College	178/1 682	0.51 (0.41, 0.62)	164/752	0.70 (0.56, 0.88)	
Men					
Education					.10
< High school	159/938	1 (Ref)	127/489	1 (Ref)	
High school	184/1 562	0.75 (0.60, 0.95)	140/668	0.89 (0.69, 1.16)	
College	173/1 738	0.59 (0.47, 0.75)	148/746	0.70 (0.54, 0.91)	
Blacks					
Education					.20
< High school	166/813	1 (Ref)	168/581	1 (Ref)	
High school	89/596	0.69 (0.53, 0.89)	77/376	0.73 (0.55, 0.96)	
College	79/635	0.48 (0.37, 0.63)	81/405	0.69 (0.52, 0.91)	
Whites					
Education					.22
< High school	239/1 306	1 (Ref)	128/445	1 (Ref)	
High school	411/3 389	0.69 (0.59, 0.82)	285/1 291	0.77 (0.62, 0.96)	
College	272/2 785	0.57 (0.48, 0.69	231/1 093	0.70 (0.56, 0.88)	

Notes: Models adjust for age, race-field site, and sex. APOE × education *p*-values derived from type III sums of squares from models with education and APOE main and interaction effects. APOE = apolipoprotein E; CI = confidence interval; HR = hazard ratio.

Our study has several limitations. The dementia diagnosis is based on multiple sources to improve our chances of observing every dementia case, and in early years hospitalization ICD codes were the only source of information. However, almost certainly some cases were missed, and our estimate of the date of dementia onset may not be accurate for all individuals. Our study was also unable to evaluate the impact of association of lower levels of education (eg, distinguishing those with no vs some primary or secondary schooling) due to the distribution of educational attainment in our data set. Substantively, however, earning a high school diploma (ie, 12 years of schooling) is a meaningful marker of education for this cohort (born 1922–1944). Likewise, separating those with one versus 2 copies of the ε4 allele was not feasible, since only 359 participants had 2 copies. Furthermore, we consider only APOE as a genetic predictor of dementia, even though several dozen common variants have been identified as influencing dementia risk above and beyond APOE (37). It is also worth noting that, among Black participants, evaluations of APOE with Alzheimer's disease and cognition have yielded inconsistent findings (21). It has previously been reported in ARIC that while APOE ε4 carriers have higher dementia risk within both race groups, APOE has a stronger effect on dementia risk among Whites participants than among Black participants (22).

We also acknowledge that our study is based on observational data, and our evaluation may be subject to measurement error (eg, diet and physical activity), and residual confounding. Furthermore, the mechanisms that explain the interaction effect between education and APOE genotype on dementia risk are unclear, and it is beyond the scope of the current study to examine these mechanisms.

It is possible that our sub-group analysis by sex and race were underpowered to detect statistically significant effects due to small sample sizes and limited variation in exposure variables within each group. Additionally, our exploratory sub-group analyses did not account for multiple comparisons. While correcting threshold *p*-values for multiple comparisons is not always advisable, not doing so may increase the potential risk for false-positive results (38).

In this study, all risk factors were measured at midlife (age 45–64). We therefore did not examine whether the timing of exposure matters for the etiological relationship between education, cardiovascular health, and dementia risk. It is important for clinical practice and public health policy to understand whether, for instance, education attained later in life has the same benefit as education attained at younger ages. Regarding cardiovascular health, it has been previously shown that midlife factors are more strongly associated with dementia risk than late-life factors; however, it is unclear whether this would alter our conclusions about the interaction of cardiovascular health with APOE. Future research should investigate these questions.

Conclusions

Among both APOE ε4 carriers and non-carriers, greater educational attainment and better cardiovascular health were associated with lower dementia incidence. These findings have important public health implications, as they provide additional evidence that genetic risk for dementia is not deterministic and add to a growing body of evidence (39) which suggests that better education and improving cardiovascular health may reduce risk of dementia, even among those with high genetic risk for the disease.

Table 4. Adjusted HR and 95% CIs of Dementia Associated with AHA Ideal Cardiovascular Health Status Stratified by APOE Genotype Carrier Status, Race, and Sex: The Atherosclerosis Risk in Communities Study (1987–2017)

	APOE ε4 Non-carriers		APOE ε4 Carriers		APOE × CVH *p*-value
	$N_{dementia}/N_{total}$	HR (95% CI)	$N_{dementia}/N_{total}$	HR (95% CI)	
Full Sample					
Cardiovascular health					.48
Poor	89/672	1 (Ref)	93/371	1 (Ref)	
Intermed.	869/6 134	0.69 (0.55, 0.86)	664/2 773	0.64 (0.51, 0.81)	
Ideal	298/2 718	0.53 (0.42, 0.68)	213/1 047	0.51 (0.39, 0.66)	
Women					
Cardiovascular health					.011
Poor	70/410	1 (Ref)	59/219	1 (Ref)	
Intermed.	487/3 191	0.64 (0.50, 0.82)	366/1 440	0.75 (0.57, 1.00)	
Ideal	183/1 685	0.50 (0.37, 0.66)	130/629	0.72 (0.51, 1.02)	
Men					
Cardiovascular health					.19
Poor	19/262	1 (Ref)	34/152	1 (Ref)	
Intermed.	382/2 943	0.84 (0.53, 1.35)	298/1 333	0.47 (0.33, 0.69)	
Ideal	115/1 033	0.66 (0.40, 1.09)	83/418	0.30 (0.20, 0.45)	
Blacks					
Cardiovascular health					.99
Poor	41/287	1 (Ref)	57/231	1 (Ref)	
Intermed	258/1 497	0.76 (0.54, 1.07)	241/1 005	0.77 (0.57, 1.03)	
Ideal	35/260	0.69 (0.43, 1.11)	28/126	0.66 (0.41, 1.05)	
Whites					
Cardiovascular health					.33
Poor	48/385	1 (Ref)	36/140	1 (Ref)	
Intermed.	611/4 637	0.63 (0.47, 0.85)	423/1 768	0.44 (0.31, 0.62)	
Ideal	263/2 458	0.48 (0.35, 0.65)	185/921	0.35 (0.24, 0.50)	

Notes: Models adjusted for age, race-field site, sex, and education. Cardiovascular health defined as poor (0–4), intermediate (5–9), or ideal (10–14) based on AHA guidelines for ideal cardiovascular health. APOE × CVH *p*-values derived from type III sums of squares from models with cardiovascular health and APOE main and interaction effects. APOE = apolipoprotein E; CI = confidence interval; HR = hazard ratio.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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M.L. conducted the data analysis and drafted the manuscript. T.M.H., K.M.G., M.E.G., S.S., J.S., and P.L.L. edited the manuscript. P.L.L. acquired funding, collected data, and designed study. The authors thank the staff and participants of the ARIC study for their important contributions.

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Conflict of Interest

None declared.

References

1. Henderson AS, Easteal S, Jorm AF, et al. Apolipoprotein E allele epsilon 4, dementia, and cognitive decline in a population sample. *Lancet*. 1995;346(8987):1387–1390. doi:10.1016/s0140-6736(95)92405-1
2. Feskens EJ, Havekes LM, Kalmijn S, de Knijff P, Launer LJ, Kromhout D. Apolipoprotein e4 allele and cognitive decline in elderly men. *BMJ*. 1994;309(6963):1202–1206. doi:10.1136/bmj.309.6963.1202
3. Myers RH, Schaefer EJ, Wilson PW, et al. Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study. *Neurology*. 1996;46(3):673–677. doi:10.1212/wnl.46.3.673
4. Laws SM, Hone E, Gandy S, Martins RN. Expanding the association between the APOE gene and the risk of Alzheimer's disease: possible roles for APOE promoter polymorphisms and alterations in APOE transcription. *J Neurochem*. 2003;84(6):1215–1236. doi:10.1046/j.1471-4159.2003.01615.x
5. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA*. 1994;271(13):1004–1010. doi:10.1001/jama.1994.03510370056032
6. Sabia S, Fayosse A, Dumurgier J, et al. Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. *BMJ*. 2019;366:l4414. doi:10.1136/bmj.l4414
7. Lahoz C, Schaefer EJ, Cupples LA, et al. Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study. *Atherosclerosis*. 2001;154(3):529–537. doi:10.1016/s0021-9150(00)00570-0
8. Seeman TE, Huang MH, Bretsky P, Crimmins E, Launer L, Guralnik JM. Education and APOE-e4 in longitudinal cognitive decline: MacArthur studies of successful aging. *J Gerontol B Psychol Sci Soc Sci*. 2005;60(2):P74–P83. doi:10.1093/geronb/60.2.p74

9. Ferrari C, Xu WL, Wang HX, et al. How can elderly apolipoprotein E ε4 carriers remain free from dementia? *Neurobiol Aging*. 2013;34(1):13–21. doi:10.1016/j.neurobiolaging.2012.03.003
10. Ngandu T, von Strauss E, Helkala EL, et al. Education and dementia: what lies behind the association? *Neurology*. 2007;69(14):1442–1450. doi:10.1212/01.wnl.0000277456.29440.16
11. Wang HX, Gustafson DR, Kivipelto M, et al. Education halves the risk of dementia due to apolipoprotein ε4 allele: a collaborative study from the Swedish brain power initiative. *Neurobiol Aging*. 2012;33(5):1007.e1–1007.e7. doi:10.1016/j.neurobiolaging.2011.10.003
12. Fenesi B, Fang H, Kovacevic A, Oremus M, Raina P, Heisz JJ. Physical exercise moderates the relationship of apolipoprotein E (APOE) genotype and dementia risk: a population-based study. *J Alzheimers Dis*. 2017;56(1):297–303. doi:10.3233/JAD-160424
13. Podewils LJ, Guallar E, Kuller LH, et al. Physical activity, APOE genotype, and dementia risk: findings from the cardiovascular health cognition study. *Am J Epidemiol*. 2005;161(7):639–651. doi:10.1093/aje/kwi092
14. Guo J, Brickman AM, Manly JJ, et al. Association of Life's Simple 7 with incident dementia and its modification by the apolipoprotein E genotype. *Alzheimers Dement J Alzheimers Assoc*. 2021. doi:10.1002/alz.12359
15. Kivipelto M, Rovio S, Ngandu T, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. *J Cell Mol Med*. 2008;12(6B):2762–2771. doi:10.1111/j.1582-4934.2008.00296.x
16. Luck T, Riedel-Heller SG, Luppa M, et al. Apolipoprotein E epsilon 4 genotype and a physically active lifestyle in late life: analysis of gene-environment interaction for the risk of dementia and Alzheimer's disease dementia. *Psychol Med*. 2014;44(6):1319–1329. doi:10.1017/S0033291713001918
17. Meng X, D'Arcy C. Apolipoprotein E gene, environmental risk factors, and their interactions in dementia among seniors. *Int J Geriatr Psychiatry*. 2013;28(10):1005–1014. doi:10.1002/gps.3918
18. Strand BH, Rosness TA, Engedal K, et al. Interaction of apolipoprotein E genotypes, lifestyle factors and future risk of dementia-related mortality: the cohort of Norway (CONOR). *Dement Geriatr Cogn Disord*. 2015;40(3-4):137–147. doi:10.1159/000431218
19. Peloso GM, Beiser AS, Satizabal CL, et al. Cardiovascular health, genetic risk, and risk of dementia in the Framingham Heart Study. *Neurology*. 2020;95(10):e1341–e1350. doi:10.1212/WNL.0000000000010306
20. Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. *JAMA Neurol*. 2017;74(10):1178–1189. doi:10.1001/jamaneurol.2017.2188
21. Barnes LL, Bennett DA. Alzheimer's disease in African Americans: risk factors and challenges for the future. *Health Aff (Millwood)*. 2014;33(4):580–586. doi:10.1377/hlthaff.2013.1353
22. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (ARIC) cohort. *JAMA Neurol*. 2017;74(10):1246–1254. doi:10.1001/jamaneurol.2017.1658
23. Boardman JD, Domingue BW, Blalock CL, Haberstick BC, Harris KM, McQueen MB. Is the gene-environment interaction paradigm relevant to genome-wide studies? The case of education and body mass index. *Demography*. 2014;51(1):119–139. doi:10.1007/s13524-013-0259-4
24. Maxwell TJ, Ballantyne CM, Cheverud JM, Guild CS, Ndumele CE, Boerwinkle E. APOE modulates the correlation between triglycerides, cholesterol, and CHD through pleiotropy, and gene-by-gene interactions. *Genetics*. 2013;195(4):1397–1405. doi:10.1534/genetics.113.157719
25. Lloyd-Jones DM, Hong Y, Labarthe D, et al; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121(4):586–613. doi:10.1161/CIRCULATIONAHA.109.192703
26. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr*. 1982;36(5):936–942. doi:10.1093/ajcn/36.5.936
27. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD; ARIC Study Investigators. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. *J Am Coll Cardiol*. 2011;57(16):1690–1696. doi:10.1016/j.jacc.2010.11.041
28. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild cognitive impairment and dementia prevalence: the atherosclerosis risk in communities neurocognitive study. *Alzheimers Dement Diagn Assess Dis Monit*. 2016;2(1):1–11. doi:10.1016/j.dadm.2015.12.002
29. McKay GJ, Silvestri G, Chakravarthy U, et al. Variations in apolipoprotein E frequency with age in a pooled analysis of a large group of older people. *Am J Epidemiol*. 2011;173(12):1357–1364. doi:10.1093/aje/kwr015
30. George KM, Lutsey PL, Kucharska-Newton A, et al. Life-course individual and neighborhood socioeconomic status and risk of dementia in the atherosclerosis risk in communities neurocognitive study. *Am J Epidemiol*. 2020;189(10):1134–1142. doi:10.1093/aje/kwaa072
31. Alonso A, Mosley TH Jr, Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. *J Neurol Neurosurg Psychiatry*. 2009;80(11):1194–1201. doi:10.1136/jnnp.2009.176818
32. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11(11):1006–1012. doi:10.1016/S1474-4422(12)70191-6
33. Jefferson AL, Gibbons LE, Rentz DM, et al. A life course model of cognitive activities, socioeconomic status, education, reading ability, and cognition. *J Am Geriatr Soc*. 2011;59(8):1403–1411. doi:10.1111/j.1532-5415.2011.03499.x
34. Wilson RS, Boyle PA, Yu L, Barnes LL, Schneider JA, Bennett DA. Life-span cognitive activity, neuropathologic burden, and cognitive aging. *Neurology*. 2013;81(4):314–321. doi:10.1212/WNL.0b013e31829c5e8a
35. Cedazo-Mínguez A. Apolipoprotein E and Alzheimer's disease: molecular mechanisms and therapeutic opportunities. *J Cell Mol Med*. 2007;11(6):1227–1238. doi:10.1111/j.1582-4934.2007.00130.x
36. Gottschalk P, Smeeding TM. Cross-national comparisons of earnings and income inequality. *J Econ Lit*. 1997;35(2):633–687. https://www.jstor.org/stable/2729789
37. van der Lee SJ, Wolters FJ, Ikram MK, et al. The effect of APOE and other common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study. *Lancet Neurol*. 2018;17(5):434–444. doi:10.1016/S1474-4422(18)30053-X
38. Althouse AD. Adjust for multiple comparisons? It's not that simple. *Ann Thorac Surg*. 2016;101(5):1644–1645. doi:10.1016/j.athoracsur.2015.11.024
39. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413–446. doi:10.1016/S0140-6736(20)30367-6