ORIGINAL RESEARCH

# Low Educational Attainment is a Predictor of Adverse Outcomes in Patients With Coronary Artery Disease

Heval M. Kelli, MD;* Anurag Mehta, MD;* Ayman S. Tahhan, MD; Chang Liu, MPH; Jeong Hwan Kim, MD; Tiffany A. Dong, MD; Devinder S. Dhindsa, MD; Bahjat Ghazzal; Muaaz K. Choudhary; Pratik B. Sandesara, MD; Salim S. Hayek, MD; Matthew L. Topel, MD, MSc; Ayman A. Alkhoder, MD; Mohamed A. Martini, MD; Arianna Sidoti; Yi-An Ko, PhD; Tene T. Lewis, PhD; Viola Vaccarino, MD, PhD; Laurence S. Sperling, MD; Arshed A. Quyyumi, MD

***Background*—**Educational attainment is an indicator of socioeconomic status and is inversely associated with coronary artery disease risk. Whether educational attainment level (EAL) among patients with coronary artery disease influences outcomes remains understudied.

***Methods and Results*—**Patients undergoing cardiac catheterization had their highest EAL assessed using options of elementary/middle school, high school, college, or graduate education. Primary outcome was all-cause mortality and secondary outcomes were a composite of cardiovascular death/non-fatal myocardial infarction and non-fatal myocardial infarction during follow-up. Cox models adjusted for clinically relevant confounders were used to analyze the association of EAL with outcomes. Among 6318 patients (63.5 years, 63% men, 23% black) enrolled, 16%, 42%, 38%, and 4% had received graduate or higher, college, high school, and elementary/middle school education, respectively. During 4.2 median years of follow-up, there were 1066 all-cause deaths, 812 cardiovascular deaths/non-fatal myocardial infarction, and 276 non-fatal myocardial infarction. Compared with patients with graduate education, those in lower EAL categories (elementary/middle school, high school, or college education) had a higher risk of all-cause mortality (hazard ratios 1.52 [95% CI 1.11–2.09]; 1.43 [95% CI 1.17–1.73]; and 95% CI 1.26 [1.03–1.53], respectively). Similar findings were observed for secondary outcomes.

***Conclusions*—**Low educational attainment is an independent predictor of adverse outcomes in patients undergoing angiographic coronary artery disease evaluation. The utility of incorporating EAL into risk assessment algorithms and the causal link between low EAL and adverse outcomes in this high-risk patient population need further investigation. **(*J Am Heart Assoc*. 2019;8: e013165. DOI: 10.1161/JAHA.119.013165.)**

**Key Words:** cardiovascular outcomes • education • risk assessment • secondary prevention • socioeconomic position

Cardiovascular disease (CVD) is the leading cause of mortality across the world and in the United States.[1] Although traditional cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and smoking are associated with atherosclerotic CVD, these factors do not fully account for the observed rates of adverse outcomes in patients with established CVD.[2] Social determinants of health, exemplified by neighborhood socioeconomic factors and individual socioeconomic status (SES) determined by income, occupation, and educational attainment level (EAL), contribute to the risk of adverse cardiovascular events in the general population.[3] It is well-established that SES has a strong inverse association with cardiovascular risk factors and risk of incident CVD in high-income countries.[4] A common indicator

*From the Emory Clinical Cardiovascular Research Institute, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA (H.M.K., A.M., A.S.T., C.L., J.H.K., D.S.D., B.G., M.K.C., P.B.S., M.L.T., A.A.A., M.A.M., A.S., Y.-A.K., V.V., L.S.S., A.A.Q.); Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA (C.L., Y.-A.K., T.T.L.); Department of Medicine, Emory University School of Medicine, Atlanta, GA (T.A.D.); Division of Cardiology, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI (S.S.H.).*

Accompanying Supplementary Data S1, Tables S1 through S4, and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013165

*Dr Kelli and Dr Mehta contributed equally to this work.

The abstract of this work was presented at the European Society of Cardiology Congress, September 3, 2019, in Paris, France.

**Correspondence to:** Arshed A. Quyyumi, MD, Emory Clinical Cardiovascular Research Institute, Emory University School of Medicine, 1462 Clifton Road Northeast, Suite 507, Atlanta, GA 30322. E-mail: aquyyum@emory.edu

Received May 2, 2019; accepted July 15, 2019.

## Clinical Perspective

### What Is New?

- Low educational attainment is directly associated with coronary artery disease risk in the general population, but the association of educational attainment level with adverse outcomes in patients with coronary artery disease is unclear.
- Our study demonstrates that educational attainment below graduate level is associated with an increased risk of mortality and cardiovascular events among patients undergoing coronary angiography for evaluation of coronary artery disease.

### What Are the Clinical Implications?

- Patients with coronary artery disease and low educational attainment are a high-risk population.
- Routine assessment of educational attainment level may help target management resources towards patients with low educational attainment, which in turn may help improve outcomes.

of SES is educational attainment, which by itself has an inverse dose-response relationship with the lifetime risk of incident CVD among asymptomatic individuals.[5] A recent mendelian randomization study has additionally established that genetic predisposition to higher educational attainment is associated with a decreased risk of coronary heart disease.[6]

The association between EAL and coronary artery disease (CAD) incidence is often thought to be mediated through modifiable lifestyle-related cardiovascular risk factors, but the exact causal link between low EAL and elevated cardiovascular risk is not completely understood.[7] Furthermore, there is a paucity of literature evaluating the association between EAL and adverse outcomes among patients with established CAD. It is plausible that similar to the association between low EAL and incident CVD among asymptomatic individuals, low educational attainment portends a worse outcome among patients with CAD. In this study, we sought to investigate the independent association of EAL with adverse cardiovascular outcomes among patients with suspected or known CAD and hypothesized that low educational attainment is an independent predictor of adverse outcomes in this high-risk patient population.

## Methods

### Study Population

The patients analyzed in this study are participants of the Emory Cardiovascular Biobank. Briefly, the Biobank is an ongoing prospective registry of adult patients undergoing cardiac catheterization for suspected or confirmed CAD at 3 Emory Healthcare affiliated hospitals in Atlanta, Georgia.[8] In the current study we included patients who were enrolled between the years 2003 and 2015. Patients with heart transplantation, severe valvular heart disease, and active cancer were excluded. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Educational Attainment Level

On a questionnaire, patients selected predefined options for their highest level of educational attainment that included: (1) elementary or middle school education, (2) high school education, (3) college education, and (4) graduate education or higher. A total of 6318 eligible patients had information available on EAL and were included in the current analysis.

### Cardiovascular Risk Factors

Patients were interviewed to collect information about demographic characteristics, medical history, medication use, and behavioral habits as previously described.[8] The prevalence of hypertension, hyperlipidemia, diabetes mellitus, prior myocardial infarction (MI), and established CAD was determined by physician diagnosis and/or treatment.[8] Medical records and *International Classification of Diseases, Ninth Revision (ICD-9)* diagnostic codes were reviewed to confirm self-reported medical history. Weight and height were measured at enrollment and body mass index was calculated by dividing weight (in kilogram) by height (in meters)-square. Left ventricular ejection fraction was abstracted after reviewing medical records and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[9] Angiographic scoring was performed using the Gensini score that quantifies CAD severity by a non-linear points system for degree of luminal narrowing and has been shown to have prognostic significance.[10] Epicardial coronary luminal narrowing $<10\%$ was designated as normal vasculature during coronary angiography.[8] The presence of an acute coronary syndrome and revascularization of any coronary artery at time of enrollment was also recorded. Overall, 0% to 9.5% participants had data missing for $\geq 1$ of the covariates listed above (details in Supplementary Data S1) and this data were assumed to be missing at random. Individual household income was not collected in this study and the median annual household income based on patients' zip code estimated using US census data is reported.[11] This study was approved by the institutional review board at Emory University (Atlanta, Georgia) and all patients provided written informed consent at the time of enrollment.

## Adverse Outcomes

Study participants were prospectively followed for the primary outcome of interest, all-cause mortality, as well as 2 secondary outcomes—a composite of cardiovascular death and non-fatal MI, and non-fatal MI events alone. Follow-up data were obtained by annual phone contact, electronic medical record review, and data from the social security death index and state records.[8] The cause of death was determined from medical record review or by direct contact with the participants' family member(s). Non-fatal MI events and cardiovascular death were adjudicated by 2 cardiologists who were blinded to study data. Non-fatal MI events were adjudicated using the third universal definition of MI,[12] and cardiovascular death was defined as death attributable to an ischemic cardiovascular cause like fatal MI, stroke or sudden death secondary to a presumed cardiovascular cause in this high-risk population.[13] Follow-up data for primary and secondary outcomes was available for 5962 (94.4%) patients and we performed a landmark analysis wherein the association of EAL with outcomes was ascertained among 5825 patients who did not experience the primary outcome within 30 days of enrollment.

## Statistical Analysis

Participant characteristics were reported as frequencies for categorical variables and means (standard deviation) or medians [25th–75th percentile] for continuous variables depending on distribution. Differences between EAL groups were assessed using the analysis of variance test for normally distributed continuous variables and the Chi-square test for categorical variables where appropriate. The Kruskal–Wallis test was used to compare non-normally distributed variables among groups.

Unadjusted Cox proportional hazards regression models were used to identify patient characteristics associated with the primary outcome. Kaplan–Meier survival curves and multivariable-adjusted Cox models were used to examine the association between EAL and all-cause mortality, composite of cardiovascular death/non-fatal MI, and non-fatal MI events. Cox models were adjusted for age, sex, race, smoking, diabetes mellitus, hypertension, hyperlipidemia, history of CAD, body mass index, left ventricular ejection fraction, eGFR, Gensini score, cardiovascular medication (aspirin, statin, beta blocker, and angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker [ARB]) use, as well as acute coronary syndrome and coronary revascularization at enrollment. We intentionally adjusted for several CVD risk factors because of the known baseline differences in risk factor burden between patients with different EAL in our cohort.[11] Missing data for covariates used in the adjusted Cox models were imputed using the Visualization and Imputation of Missing values R package by using the k-nearest neighbors approach.[14] Additionally, the effect of unmeasured confounders on these associations was estimated by computing E-values.[15]

We further adjusted Cox models for zip-code based estimated annual income as a sensitivity analysis. We also evaluated the association of EAL with outcomes after excluding patients with normal epicardial coronary arteries on angiography (<10% angiographic stenosis) in a separate model. The multiplicative interaction of several clinical covariates (age [dichotomized at 65 years], sex, race, diabetes mellitus, hypertension, smoking, hyperlipidemia, eGFR [dichotomized at 60 mL/min per 1.73 $m^2$], BMI [dichotomized at 30 $kg/m^2$], history of CAD, acute coronary syndrome at enrollment, and coronary revascularization at enrollment) with EAL dichotomized at graduate education for predicting all-cause mortality was tested in adjusted Cox models as well. Lastly, we classified patients into 4 mutually exclusive groups based on EAL dichotomized at college education and history of prior MI to study the joint association of EAL and prior MI with the primary outcome using Kaplan–Meier survival curves.

All analyses were performed using IBM SPSS Statistics Version 25 (Armonk, NY) and R version 3.3.3 (R Foundation for statistical computing, Vienna, Austria). Two-tailed $P<0.05$ were considered statistically significant. The STROBE statement for this observational cohort study is provided in Table S1.

# Results

## Patient Characteristics

Baseline demographic and clinical characteristics of study patients stratified by EAL are presented in Table 1. The study cohort was 63% men, 23% black, with a mean age of 63.5 years. The highest EAL was graduate or higher level of education and was observed in 16% patients, while 42% obtained college education, 38% had a high school diploma, and 4% had an elementary or middle school education (Table 1). Patients with lower EAL were older, more frequently women, black, and had a higher prevalence of smoking, diabetes mellitus, hypertension, history of CAD, and had a higher Gensini score along with a lower left ventricular ejection fraction, eGFR, and estimated annual income as compared with patients with higher EAL (Table 1). Normal coronary arteries were observed in 11% of the study cohort and EAL has an inverse association with its prevalence (Table 1).

## Adverse Cardiovascular Outcomes

Patients who did not experience the primary outcome within 30 days of enrollment and had adjudicated outcomes data

**Table 1.** Baseline Characteristics of Participants Stratified by Level of Educational Attainment

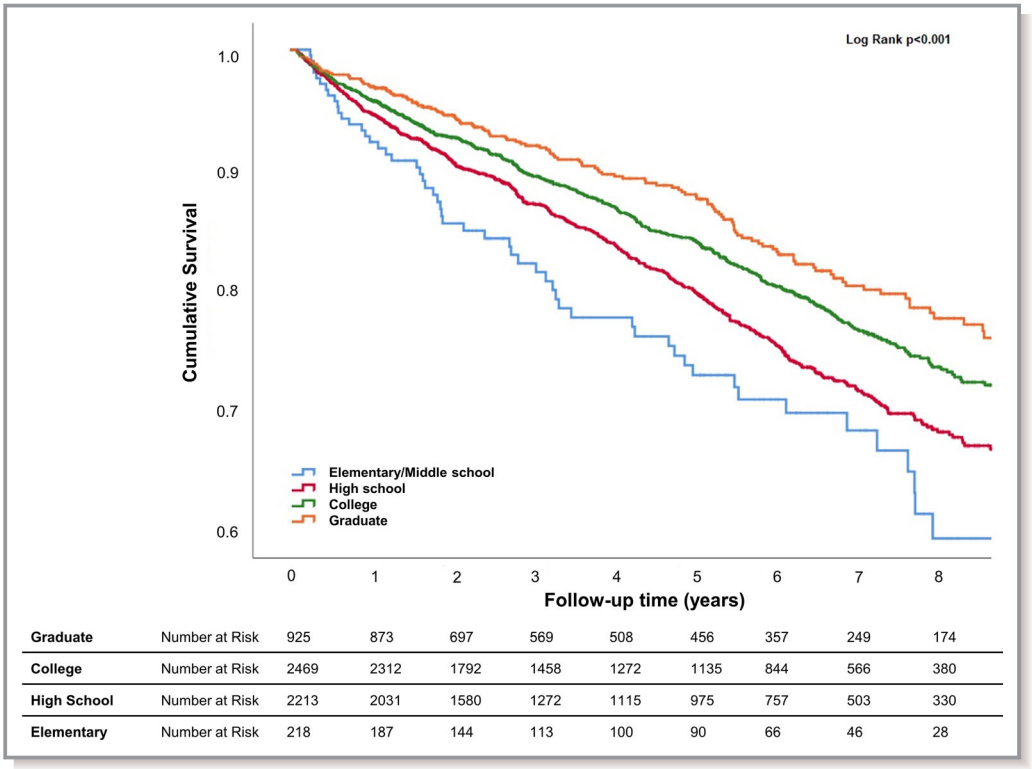
| Participant Characteristics | All Patients (n=6318) | Elementary/Middle School Education (n=228) | High School Education (n=2403) | College Education (n=2689) | Graduate Education (n=998) | *P* Value |
|---|---|---|---|---|---|---|
| Age, y | 63.5 (12.2) | 67.4 (12.0) | 63.6 (12.0) | 62.9 (12.3) | 64.2 (12.0) | <0.001 |
| Men | 3995 (63.2) | 135 (59.2) | 1402 (58.3) | 1719 (63.9) | 739 (74.0) | <0.001 |
| Black race | 1470 (23.3) | 62 (27.2) | 604 (25.1) | 620 (23.1) | 184 (18.4) | <0.001 |
| Ever smoking | 4071 (64.4) | 162 (71.1) | 1649 (68.6) | 1664 (61.9) | 596 (59.7) | <0.001 |
| Diabetes mellitus | 2193 (34.9) | 99 (43.4) | 895 (37.5) | 887 (33.2) | 312 (31.3) | <0.001 |
| Hypertension | 4945 (78.6) | 188 (83.2) | 1932 (80.7) | 2096 (78.3) | 729 (73.3) | <0.001 |
| Hyperlipidemia | 4476 (71.2) | 168 (74.3) | 1707 (71.3) | 1905 (71.1) | 696 (70.1) | 0.637 |
| History of myocardial infarction | 1463 (23.4) | 75 (33.2) | 602 (25.3) | 587 (22.1) | 199 (20.3) | <0.001 |
| History of coronary artery disease | 4774 (75.6) | 190 (83.3) | 1851 (77.0) | 1983 (73.7) | 750 (75.2) | 0.002 |
| Body mass index, kg/m$^2$ | 29.8 (6.8) | 29.5 (6.5) | 29.9 (6.5) | 30.1 (7.23) | 29.2 (6.1) | 0.010 |
| Left ventricular ejection fraction (%) | 52.8 (12.8) | 50.6 (13.5) | 55.0 (13.1) | 53.2 (12.7) | 52.9 (12.3) | 0.015 |
| eGFR, mL/min per 1.73 m$^2$ | 73.0 (24.4) | 69.5 (23.9) | 72.1 (249) | 74.0 (24.3) | 73.6 (23.4) | 0.005 |
| ACS at enrollment | 1165 (18.4) | 49 (21.5) | 454 (18.9) | 478 (17.8) | 184 (18.4) | 0.470 |
| Normal coronaries on angiogram | 698 (11.0) | 12 (5.3) | 246 (10.2) | 314 (12.7) | 126 (12.6) | 0.005 |
| Gensini score | 7.5 [0.0–35.5] | 8.3 [0.0–29.9] | 8.0 [0.0–37.5] | 6.0 [0.0–33.5] | 8.0 [0.0–39.0] | 0.035 |
| Revascularization at enrollment | 2210 (35.0) | 84 (36.8) | 865 (36.0) | 927 (34.5) | 334 (33.5) | 0.432 |
| Estimated annual income (US dollars) | 46 646 [37 109–60 428] | 40 982 [35 433–50 983] | 42 902 [36 465–53 818] | 48 210 [38 852–63 338] | 52 167 [40 982–67 335] | <0.001 |
| Aspirin use | 4727 (74.8) | 173 (75.9) | 1781 (74.1) | 1988 (73.9) | 785 (78.7) | 0.021 |
| Statin use | 4407 (69.8) | 169 (74.1) | 1637 (68.1) | 1854 (68.9) | 747 (74.8) | <0.001 |
| Beta blocker use | 4207 (66.6) | 161 (70.6) | 1641 (68.3) | 1718 (63.9) | 687 (68.8) | 0.001 |
| ACE inhibitor/ARB use | 3457 (54.7) | 137 (60.1) | 1314 (54.7) | 1458 (54.2) | 548 (54.9) | 0.401 |

Values shown are number (percentage) and mean (standard deviation) for normally distributed variables or median [25th–75th percentile] for non-normally distributed variables. ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

available for analysis were followed for a median duration of 4.2 [1.8–6.8] years. There were 1066 all-cause deaths, 812 cardiovascular deaths/non-fatal MI and 276 non-fatal MI events. Older age, smoking, diabetes mellitus, hypertension, history of CAD, and Gensini score were directly associated; while BMI, left ventricular ejection fraction, eGFR, and estimated annual income were inversely associated with all-cause mortality in study patients (Table S2).

## Educational Attainment Level and Adverse Outcomes

Kaplan–Meier survival curves for the association between EAL and all-cause mortality are shown in Figure 1. The cumulative survival for study participants decreased across categories of graduate, college, high school, and elementary/middle school education. A similar trend was observed for the secondary outcomes of cardiovascular death/non-fatal MI and non-fatal MI events (Figure 2A and 2B). In unadjusted Cox proportional hazards regression analyses, patients with elementary/middle school, high school, or college education had a 104%, 57%, and 24% higher risk of all-cause mortality compared with those with graduate education, respectively. Similarly, there was a significantly higher hazard for the secondary outcomes of cardiovascular death/non-fatal MI and non-fatal MI among those with elementary/middle school and high school education compared with graduate education level (Table 2).




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Graduate** | Number at Risk | 925 | 873 | 697 | 569 | 508 | 456 | 357 | 249 | 174 |
| **College** | Number at Risk | 2469 | 2312 | 1792 | 1458 | 1272 | 1135 | 844 | 566 | 380 |
| **High School** | Number at Risk | 2213 | 2031 | 1580 | 1272 | 1115 | 975 | 757 | 503 | 330 |
| **Elementary** | Number at Risk | 218 | 187 | 144 | 113 | 100 | 90 | 66 | 46 | 28 |

**Figure 1.** Association between level of educational attainment and all-cause mortality. Kaplan–Meier curves for categories of graduate, college, high school, and elementary/middle school education. The cumulative survival of study participants progressively decreased across categories of educational attainment level, with the highest all-cause mortality risk observed among those with elementary/middle school education.

After adjustment for demographic characteristics, risk factors, angiographic CAD severity, cardiovascular medications, and revascularization at enrollment the inverse association between EAL and all-cause mortality remained statistically significant (Table 2). Thus, compared with patients with graduate education, those with elementary/middle school, high school, or college education had a 52%, 43%, and 26% increased risk of all-cause mortality, respectively (Table 2). Sensitivity analyses for this observation were performed by computing the E-value and these results are reported in Supplementary Data S1. The significant unadjusted associations between EAL categories of elementary/middle school and high school education and the secondary outcomes remained significant after multivariate adjustment as well (Table 2).

## Sensitivity Analyses

The independent association between EAL categories and all-cause mortality was not attenuated after Cox models were further adjusted for estimated annual income (Table S3). Furthermore, after excluding participants with normal coronary arteries the association of elementary/middle school and high school education with the primary and secondary outcomes remained significant (Table S4). EAL dichotomized at graduate education was also independently associated with all-cause mortality (hazard ratio 1.31, 95% CI 1.09–1.57). We found no significant heterogeneity in this relationship based on age, race, diabetes mellitus, hypertension, smoking, hyperlipidemia, BMI, history of CAD, ACS at enrollment, and revascularization at enrollment (Figure 3). However, the association of EAL and all-cause mortality was significantly modified by sex (*P*-interaction=0.044) and by renal function impairment (eGFR <60 mL/min per 1.73 $m^2$, *P*-interaction=0.044), such that the strength of this association was stronger among women and among patients with preserved renal function as compared with men and those with renal function impairment, respectively (Figure 3).

Lastly, we classified study participants into 4 mutually exclusive groups based on EAL dichotomized at college education and history of prior MI. Among patients with EAL below college education, 26% had a history of prior MI and the corresponding proportion among those with EAL above college education was 22%. Patients without college education and prior history of MI had the highest risk for all-cause mortality during follow-up. Notably, all-cause mortality incidence among patients with college education and prior MI was similar to patients with a lack of college education and without prior MI (Figure S1).

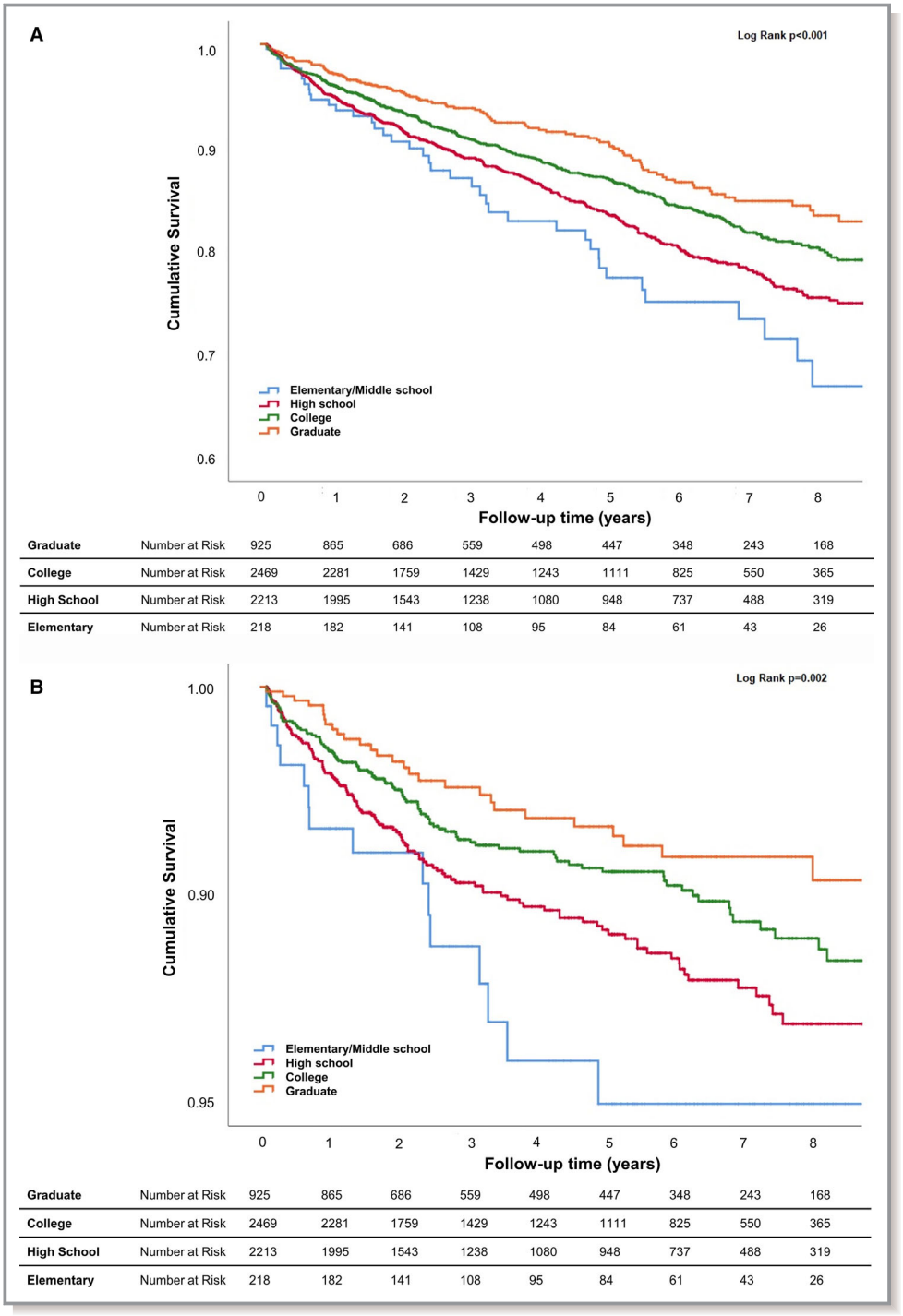



**Figure 2.** Association of level of educational attainment with composite of cardiovascular death/non-fatal myocardial infarction (**A**) and non-fatal myocardial infarction (**B**). Kaplan–Meier curves for categories of graduate, college, high school, and elementary/middle school education. The cumulative survival of study participants from cardiovascular death/non-fatal myocardial infarction and non-fatal myocardial infarction progressively decreased across categories of educational attainment level with the highest risk observed among those with elementary/middle school education.

## Discussion

In this large cohort study of patients undergoing cardiac catheterization for evaluation of CAD we report several important findings. First, we demonstrated that lower EAL predicts adverse cardiovascular outcomes and this inverse association was persistent and graded throughout various levels of educational attainment from elementary/middle

**Table 2.** Association Between Level of Educational Attainment and Adverse Outcomes

| | | All-Cause Mortality | | Cardiovascular Death/Nonfatal MI | | Nonfatal MI | |
|---|---|---|---|---|---|---|---|
| | Educational Level | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| Unadjusted | Elementary/Middle school | 2.04 (1.49–2.79) | <0.001 | 2.01 (1.40–2.90) | <0.001 | 2.40 (1.32–4.37) | 0.004 |
| | High school | 1.57 (1.29–1.90) | <0.001 | 1.56 (1.25–1.95) | <0.001 | 1.69 (1.15–2.50) | 0.004 |
| | College | 1.24 (1.02–1.51) | 0.032 | 1.24 (0.99–1.55) | 0.062 | 1.27 (0.86–1.89) | 0.235 |
| | Graduate | Referent | | Referent | | Referent | |
| Adjusted* | Elementary/Middle school | 1.52 (1.11–2.09) | 0.010 | 1.46 (1.02–2.11) | 0.041 | 1.84 (1.01–3.38) | 0.048 |
| | High school | 1.43 (1.17–1.73) | <0.001 | 1.38 (1.10–1.73) | 0.005 | 1.49 (1.004–2.20) | 0.048 |
| | College | 1.26 (1.03–1.53) | 0.023 | 1.24 (0.99–1.56) | 0.060 | 1.25 (0.84–1.86) | 0.273 |
| | Graduate | Referent | | Referent | | Referent | |

Survival analysis for 5825 participants—218 elementary/middle school education (55 all-cause deaths, 41 cardiovascular death/non-fatal MI, and 16 non-fatal MI), 2213 high school education (463 all-cause deaths, 352 cardiovascular death/non-fatal MI, and 123 non-fatal MI), 2469 college education (415 all-cause deaths, 318 cardiovascular death/non-fatal MI, and 105 non-fatal MI), and 925 graduate education (133 all-cause deaths, 101 cardiovascular death/non-fatal MI, and 32 non-fatal MI). HR indicates hazard ratio; MI, myocardial infarction. *Model adjusted for age, sex, race, ever smoking, diabetes mellitus, hypertension, hyperlipidemia, history of coronary artery disease, body mass index, left ventricular ejection fraction, estimated glomerular filtration rate, Gensini score, cardiovascular medication (aspirin, statin, beta blocker, and ACE inhibitor/ARB) use, acute coronary syndrome and coronary revascularization at enrollment.

school, high school, college, to graduate education; with the highest adjusted risk observed in those with the lowest EAL. Second, the impact of EAL on the primary outcome of all-cause mortality was independent of estimated annual income which is another marker of SES. Third, EAL below graduate education was independently associated with all-cause mortality and the strength of this association was higher among women and those without renal function impairment. Lastly, the impact of having an EAL below college education was similar to having a history of prior MI, such that the all-cause mortality incidence was similar in patients who were college educated and had a prior MI as those who were not college educated but had no history of MI.

Level of educational attainment is known to be associated with traditional cardiovascular risk factors among asymptomatic individuals living in heterogeneous socioeconomic conditions.[16] Indeed, it has been shown that nearly half of the CVD risk conferred by low educational attainment is mediated by behavioral and biological risk factors.[17] Herein, we confirmed this increased prevalence of cardiovascular risk factors in our cohort of patients undergoing evaluation of CAD. Our results indicate that there is a graded decline in prevalent cardiovascular risk factors including smoking, hypertension, and diabetes mellitus across the spectrum of increasing EAL. Moreover, we found that the prevalence of established CAD and CAD severity was higher among patients with low EAL.

Previous studies in the general population without known CVD have also revealed an inverse relationship between educational attainment and risk of adverse cardiovascular outcomes.[18–21] A meta-analysis by Manrique-Garcia et al showed that lower educational attainment was associated with a pooled 34% increased risk of developing an acute MI.[20] In an updated meta-analysis, Khaing et al reported that low EAL was associated with a 23% to 39% increased risk of stroke, CAD, and cardiovascular death.[21] Our study is unique in that it is the first to show an inverse relationship between EAL and adverse outcomes in a large cohort of patients undergoing invasive evaluation of CAD even after demographic characteristics, cardiovascular risk factors, angiographic CAD severity, cardiovascular medications, and coronary revascularization are accounted for.

The increased strength of association between EAL below graduate education and mortality among women merits attention. Low educational attainment is known to be an independent predictor for fatal CVD events among women with established CVD.[22] However, no study to date has explored the sex-based differential impact of EAL on survival among patients with suspected or confirmed CAD. Our data suggest that the survival benefit afforded by higher EAL among these patients is heightened among women as compared with men. The reasons for this observation are unclear and it is possible that women with low EAL are more prone to having sub-optimal preventive lifestyle behaviors, medication non-adherence, mental stress, depression, and poor access to care as compared with men. We additionally observed that the EAL below graduate education and all-cause mortality association was modified by renal function with a stronger association seen among patients without renal function impairment. Chronic kidney disease (eGFR below 60 mL/min per 1.73 $m^2$) has been recognized as a "high-risk condition" among patients with established CVD in the current American cholesterol management guidelines.[23] Our data show that EAL below graduate education retains its

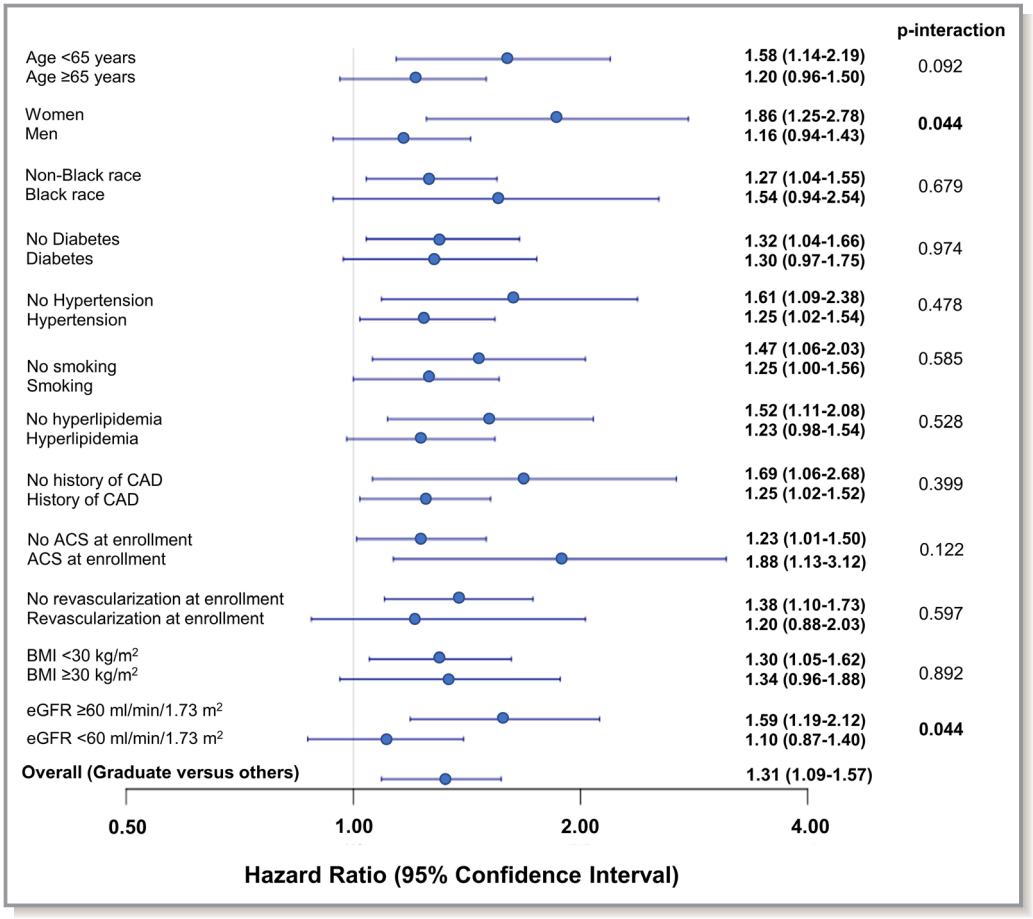



**Figure 3.** Interaction between educational attainment level dichotomized at graduate education and clinical characteristics for risk of all-cause mortality. Cox proportional hazards regression model to ascertain the association between educational attainment level dichotomized at graduate education and all-cause mortality. Model adjusted for age (dichotomized at 65 years), sex, race, diabetes mellitus, hypertension, ever smoking, hyperlipidemia, eGFR (dichotomized at 60 mL/min per 1.73 $m^2$), BMI (dichotomized at 30 $kg/m^2$), left ventricular ejection fraction, history of CAD, Gensini score, cardiovascular medication (aspirin, statin, beta blocker, and angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker) use, ACS at enrollment, and coronary revascularization at enrollment. The relationship was significantly modified by sex and by renal function, such that the association was attenuated among men and participants with renal function impairment. ACS indicates acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate.

independent predictive value among patients who do not harbor this high-risk condition.

It is also well-established that household income and EAL are 2 core components of SES and a previous study from the Stanford 5-city project revealed that these measures are correlated, but EAL had a stronger association with traditional cardiovascular risk factors like smoking, blood pressure, and serum cholesterol.[18] A more recent analysis from the REGARDS (Reasons for Geographic And Racial Differences in Stroke) study showed that both low household income and EAL have an additive joint association for predicting CVD risk among asymptomatic individuals.[24] Notably, in the meta-analysis by Khaing and colleagues the effect size of the pooled estimate of the association of low income and low EAL with adverse outcomes was similar.[21] Herein, we did not collect information about individual household income and leveraged information from patients' zip-code of residence to obtain estimated median annual income for the patients' neighborhood. Importantly, we observed that the association between EAL and the primary outcome was not attenuated after adjusting for estimated income.

The mechanisms underlying the association between educational attainment and cardiovascular outcomes are likely multifactorial and involve a complex interplay of poor health literacy exacerbating unhealthy lifestyle habits and medication non-compliance.[16] Without the necessary

education to motivate change, unhealthy behaviors are more likely to persist, increasing the risk of CVD among poorly educated individuals compared with their more educated counterparts. Thus, even after undergoing cardiac catheterization, patients with low EAL may not realize that continuing behavioral habits like smoking puts them at a higher risk for future events. This was evident in our cohort where a significantly higher proportion of patients with elementary/middle school education were smokers as compared with patients with graduate education. Patients with lower EAL are also likely to have poorer access to health care and such disparity is likely driven by multiple factors including financial barriers. These patients are more likely to present with advanced stages of chronic medical conditions compared with patients with more years of schooling. Herein, we show that even within those with suspected or confirmed CAD and high burden of traditional risk factors, low EAL independently identifies those with even higher risk of future adverse events.

## Strengths

Our study has several strengths. We have evaluated the association between EAL and cardiovascular outcomes in a region of the United States where there is significant racial and regional disparity in the incidence of CVD. Unlike a number of previously published population-based studies of asymptomatic individuals our study investigated a population with a high prevalence of established CAD. Our study sample is large and with nearly 1100 deaths recorded during follow-up we are adequately powered to study the impact of EAL on adverse outcomes in a high-risk patient population.

## Limitations

This study should be interpreted in the context of its limitations. We report findings from a single center study of an urban, high-risk southeastern US patient population and our cohort's EAL is significantly higher than the national average as reported by the US Census Bureau,[25] which limits the generalizability of our findings. Our study participants were referred for cardiac catheterization and might have received more intensive follow-up after the procedure, however, this is likely to have been similar in all EAL subsets. Despite this possibility, we were found an independent association between EAL and adverse outcomes in our cohort. The association of EAL with outcomes was assessed after controlling for prevalent cardiovascular risk factors, but the time duration of harboring these risk factors as well as change in risk factor levels and preventive medications over time has not been accounted for. Also, we did not gather data on individual household income and insurance status which could influence access to health care in this population and in turn affect patient outcomes. Lastly, although we have adjusted for multiple confounders and performed several sensitivity analyses, the possibility of residual confounding cannot be completely excluded given the observational nature of this study.

## Conclusions

In patients undergoing cardiac catheterization for evaluation of CAD, EAL was independently associated with adverse outcomes both in overall mortality and cardiovascular events. Routine assessment of EAL among such patients may help guide management decisions and targeting of specific resources towards those with low EAL to improve outcomes. Additional studies are warranted to evaluate the impact of incorporating EAL into risk assessment algorithms for patients with CAD and to clarify the causative link between low education level and adverse cardiovascular outcomes.

## Acknowledgments

The authors would like to acknowledge the Emory Cardiovascular Biobank participants and research study coordinators.

## Sources of Funding

Drs Kelli, Mehta, Tahhan, Kim, Dhindsa, and Sandesara have been supported by the Abraham J. & Phyllis Katz Foundation. Dr Kelli has been supported by NHLBI T32 THL130025A grant. Dr Mehta is supported by American Heart Association grant 19POST34400057. Dr Quyyumi is supported by NIH grants 1R61HL138657-02, 1P30DK111024-03S1, 5R01HL095479-08, 3RF1AG051633-01S2, 5R01AG042127-06, 2P01HL086773-08, U54AG062334-01, 1R01HL141205-01, 5P01HL101398-02, 1P20HL113451-01, 5P01HL086773-09, 1RF1AG051633-01, R01 NS064162-01, R01 HL89650-01, HL095479-01, 1DP3DK094346-01, 2P01HL086773, and American Heart Association grant 15SFCRN23910003.

## Disclosures

None.

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# Supplemental Material

**Data S1.**

**Missing data**

Number of participants (out of 6,318) with missing data – diabetes (32), hypertension (25), hyperlipidemia (28), history of MI (68), body mass index (446), ejection fraction (503), normal coronaries on angiogram (548), Gensini score (603), estimated income (1,280), and primary or secondary cardiovascular outcome (356). Complete data was available for rest of the covariates.

**E-value**

The E-value is defined as the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure/outcome association, conditional on the measured covariates.(1)

In the analysis of the association between educational attainment level and all-cause mortality the observed hazard ratios of 1.52, 1.43, and 1.26 for elementary/middle school, high school, and college education, respectively, could be explained away by an unmeasured confounder that was associated with both the educational attainment level and the all-cause mortality by a hazard ratio of 2.01, 1.88, and 1.63 each, respectively, above and beyond the measured confounders, but weaker confounding could not do so. Similarly, the corresponding confidence intervals could be moved to include the null by an unmeasured confounder that was associated with both the educational attainment level and the all-cause mortality by a hazard ratio of 1.36, 1.47, and 1.17 each, above and beyond the measured confounders, but weaker confounding could not do so.

**Table S1. STROBE Statement - Checklist of items that should be included in reports of cohort studies.**

| | Item No. | Recommendation | Page No. |
|---|---|---|---|
| **Title and abstract** | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 3, 4 |
| **Introduction** | | | |
| Background/ rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5, 6 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6, 7 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |

| | | | |
|---|---|---|---|
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 6, 7 |
| | | (b) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6, 7, 8 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).* Describe comparability of assessment methods if there is more than one group (*Give information separately for exposed and unexposed) | 6, 7, 8 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 8, 9 |
| Study size | 10 | Explain how the study size was arrived at | 6, 7, 8 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6, 7, 8 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | 8, 9 |

| | | | |
|---|---|---|---|
| | | (b) Describe any methods used to examine subgroups and interactions | 9 |
| | | (c) Explain how missing data were addressed | 8 |
| | | (d) If applicable, explain how loss to follow-up was addressed | 8 |
| | | (e) Describe any sensitivity analyses | 8, 9 |
| **Results** | | | |
| Participants | 13 | (a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed | 6, 8 |
| | | (b) Give reasons for non-participation at each stage | 6, 7, 8 |
| | | (c) Consider use of a flow diagram | Not done |
| Descriptive data | 14 | (a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Supplement |
| | | (c) Summarize follow-up time (e.g., average and total amount) | 10 |
| Outcome data | 15 | Report numbers of outcome events or summary measures over time | 10, Table 2 |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates | Table 2 |

| | | | |
|---|---|---|---|
| | | and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Supplement Table 2 |
| | | (b) Report category boundaries when continuous variables were categorized | Figure 3 |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Not done |
| Other analyses | 17 | Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses | 11, 12 Figure 3 |
| **Discussion** | | | |
| Key results | 18 | Summarize key results with reference to study objectives | 12 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 16 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 16 |
| Generalizability | 21 | Discuss the generalizability (external validity) of the study results | 16 |
| **Other** | | | |

| | | | |
|---|---|---|---|
| **information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 1 |

**Table S2. Association of clinical characteristics with all-cause mortality.**

| Participant Characteristics | Hazard Ratio (95% Confidence Interval) | p-value |
|---|---|---|
| Age (per 10 years increase) | 1.51 (1.42-1.60) | <0.001 |
| Male sex | 1.07 (0.94-1.21) | 0.299 |
| Black race | 1.12 (0.96-1.31) | 0.140 |
| Ever smoking | 1.28 (1.12-1.46) | <0.001 |
| Diabetes | 1.49 (1.32-1.68) | <0.001 |
| Hypertension | 1.44 (1.23-1.68) | <0.001 |
| Hyperlipidemia | 1.13 (0.99-1.28) | 0.071 |
| History of coronary artery disease | 1.67 (1.42-1.96) | <0.001 |
| History of myocardial infarction | 1.28 (1.12-1.46) | <0.001 |
| Body mass index (per $kg/m^2$) | 0.96 (0.95-0.97) | <0.001 |
| Left ventricular ejection fraction (per 5% increase) | 0.85 (0.83-0.87) | <0.001 |
| eGFR (per 10 ml/min/1.73 $m^2$ increase) | 0.79 (0.78-0.81) | <0.001 |
| Gensini score (per unit increase) | 1.004 (1.003-1.005) | <0.001 |

| | | |
|---|---|---|
| ACS at enrollment | 1.16 (0.98-1.37) | 0.088 |
| Revascularization at enrollment | 0.91 (0.80-1.04) | 0.158 |
| Estimated annual income (per 10,000 US dollars) | 0.91 (0.88-0.95) | <0.001 |

eGFR = estimated glomerular filtration rate, ACS = acute coronary syndrome

**Table S3. Association between level of educational attainment and adverse outcomes after adjusting for estimated annual income.**

| | All-cause mortality | | Cardiovascular death/nonfatal MI | | Nonfatal MI | |
|---|---|---|---|---|---|---|
| **Educational Level** | **HR (95%CI)** | **p-value** | **HR (95%CI)** | **p-value** | **HR (95%CI)** | **p-value** |
| Elementary/Middle school | 1.46 (1.06-2.00) | 0.021 | 1.39 (0.96-2.00) | 0.081 | 1.72 (0.94-3.16) | 0.081 |
| High school | 1.38 (1.14-1.68) | 0.001 | 1.32 (1.06-1.66) | 0.015 | 1.39 (0.94-2.07) | 0.103 |
| College | 1.24 (1.02-1.51) | 0.033 | 1.22 (0.97-1.53) | 0.086 | 1.22 (0.82-1.81) | 0.336 |
| Graduate | Referent | | Referent | | Referent | |

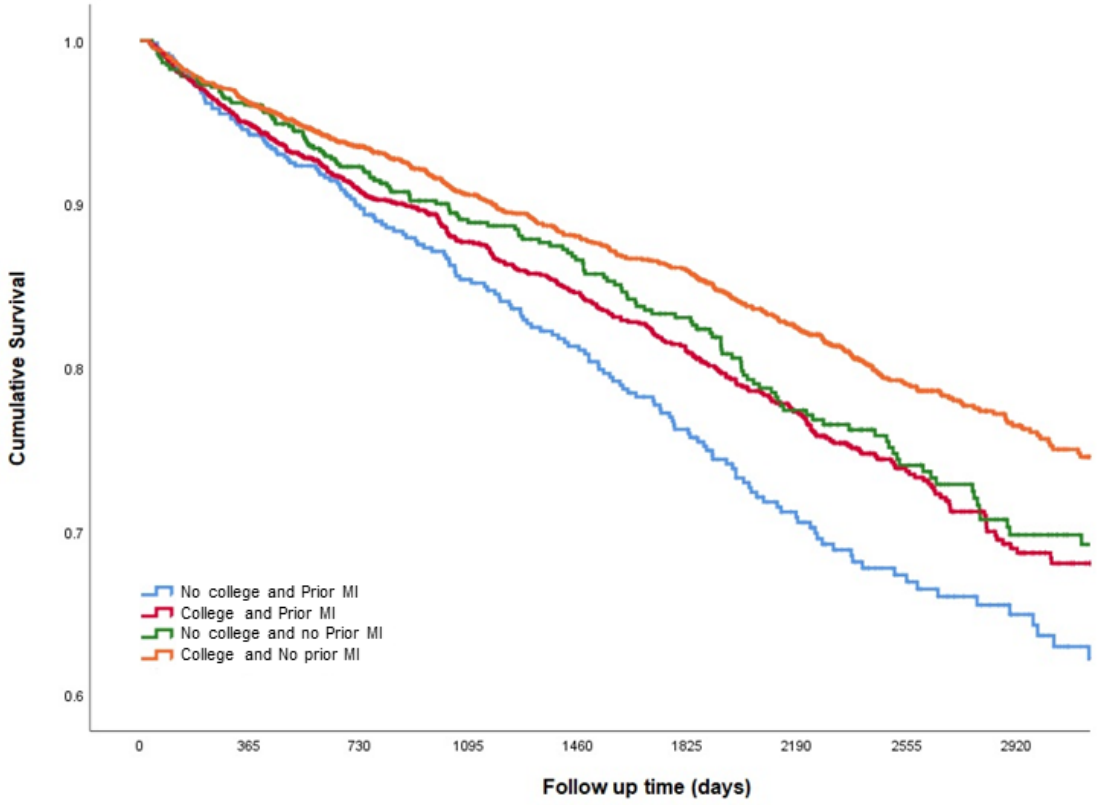
Model adjusted for age, sex, race, ever smoking, diabetes, hypertension, hyperlipidemia, history of coronary artery disease, body mass index, left ventricular ejection fraction, estimated glomerular filtration rate, Gensini score, cardiovascular medication (aspirin, statin, beta blocker, and ACE inhibitor/ARB) use, estimated annual income, acute coronary syndrome and coronary revascularization at enrollment. HR: hazard ratio, MI: myocardial infarction

**Table S4. Association between level of educational attainment and adverse outcomes after excluding patients with normal epicardial coronary arteries (epicardial coronary artery luminal narrowing <10%).**

| | All-cause mortality | | Cardiovascular death/nonfatal MI | | Nonfatal MI | |
|---|---|---|---|---|---|---|
| **Educational Level** | **HR (95%CI)** | **p-value** | **HR (95%CI)** | **p-value** | **HR (95%CI)** | **p-value** |
| Elementary/Middle school | 1.41 (1.02-1.95) | 0.040 | 1.41 (1.02-1.95) | 0.040 | 1.87 (1.02-3.44) | 0.044 |
| High school | 1.34 (1.09-1.63) | 0.005 | 1.34 (1.09-1.63) | 0.005 | 1.49 (1.003-2.22) | 0.048 |
| College | 1.19 (0.97-1.46) | 0.091 | 1.19 (0.97-1.46) | 0.091 | 1.22 (0.81-1.82) | 0.341 |
| Graduate | Referent | | Referent | | Referent | |

Model adjusted for age, sex, race, ever smoking, diabetes, hypertension, hyperlipidemia, history of coronary artery disease, body mass index, left ventricular ejection fraction, estimated glomerular filtration rate, Gensini score, cardiovascular medication (aspirin, statin, beta blocker, and ACE inhibitor/ARB) use, acute coronary syndrome and coronary revascularization at enrollment. HR: hazard ratio, MI: myocardial infarction

**Figure S1. Association of history of myocardial infarction and educational attainment dichotomized at college education with all-cause mortality.**




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| College No Prior MI | Number at Risk | 2607 | 2426 | 1895 | 1543 | 1350 | 1214 | 908 | 602 | 399 |
| College Prior MI | Number at Risk | 744 | 682 | 536 | 438 | 386 | 342 | 263 | 189 | 133 |
| No College No Prior MI | Number at Risk | 1775 | 1597 | 1231 | 970 | 841 | 737 | 583 | 378 | 244 |
| No College Prior MI | Number at Risk | 633 | 565 | 450 | 374 | 332 | 293 | 214 | 152 | 100 |

Kaplan–Meier curves for categories of college education/no prior MI, below college education/no prior MI, college education/prior MI, and below college education/prior MI. Cumulative survival among patients with college education and prior MI was similar to patients with a lack of college education and no prior MI. The highest incidence of all-cause mortality was observed among patients without college education and prior history of MI. MI = myocardial infarction.

**Supplemental Reference:**

1. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med.* 2017;167:268-274.