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Association of educational attainment with cancer mortality in a national cohort study of black and white adults: A mediation analysis

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ABSTRACT

Background: Low educational attainment is associated with excess cancer mortality. However, the mechanisms driving this association remain unknown.

Methods: Using data from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, we evaluated the associations of participant and parental/caregiver education with cancer mortality using Cox proportional hazards models, adjusting for socio-demographic characteristics and health conditions. We used principal components analysis to generate indices of measures representing the social determinants of health (SDOH) and health behaviors. We used structural equation modeling to determine if the association between educational attainment and cancer mortality was mediated by these domains.

Results: Among 30,177 REGARDS participants included in this analysis, 3798 (12.6%) had less than a high school degree. In fully adjusted models, those without a high school education experienced about 50% greater risk of death than high school graduates and higher (White participants HR: 1.47; 95% CI: 1.23, 1.76 and Black HR: 1.54; 95% CI: 1.33, 1.79). There was evidence of a modest mediation effect for the association between education and cancer mortality by the SDOH domain score (White total effect HR: 1.25; 95% CI: 1.18, 1.33, indirect effect HR: 1.04; 95% CI: 1.03, 1.05, direct effect HR: 1.21; 95% CI: 1.14, 1.28 and Black total effect HR: 1.24; 95% CI: 1.18, 1.29, indirect effect HR: 1.04; 95% CI: 1.03, 1.05, direct effect HR: 1.19; 95% CI: 1.14, 1.24). There was no evidence of mediation by the health behaviors score. No significant associations were found for female caregiver/mother's or male caregiver/father's education (N = 13,209).

Conclusions: In conclusion, participant education was strongly associated with cancer mortality, and this association was partially mediated by the SDOH domain score.

1. Introduction

Cancer is the second leading cause of death in the United States; there were an estimated 1.9 million cases diagnosed and 0.6 million cancer-related deaths in 2021 (Siegel et al., 2021). The highest mortality burden is from cancers of the lung, prostate, and colorectum in men, and cancers of the lung, breast, and colorectum in women; many of these cancers are preventable (Siegel et al., 2021). Educational attainment is well understood to be a fundamental social determinant of health (SDOH) (Hahn & Truman, 2015; Zajacova & Lawrence, 2018), with several studies noting that lower individual education is associated with higher cancer stage at diagnosis (Liu et al., 2017; Singh et al., 2004) and cancer-specific mortality (Albano et al., 2007; Barcelo et al., 2021; Coughlin, 2020). In addition to individual educational attainment, parental/caregiver education level may also impact cancer mortality outcomes, although associations are inconsistent. For example, Pudrovska and Anikputa found that higher father's education was related to lower breast cancer mortality in the United States (Pudrovska & Anikputa, 2012). However, a recent systematic review noted that four studies in Europe provided little evidence of an association between

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early-life socioeconomic position and breast cancer mortality (Akinyemiju et al., 2018). Further research is needed to clarify the role of parental education in cancer mortality in the United States.

Educational attainment may influence cancer mortality outcomes via other SDOHs, such as the social environment, income level, and healthcare access (Hahn & Truman, 2015; Zajacova & Lawrence, 2018). Indeed, several studies have shown that having a low income (Singh & Jemal, 2017), receiving care at lower volume healthcare facilities (Bristow et al., 2014; Greenup et al., 2018), living in an impoverished area (Singh & Jemal, 2017; O'Connor et al., 2018), and lacking health insurance (Cole et al., 2019; Mohamed et al., 2020) are all associated with increased cancer mortality. Furthermore, Pinheiro et al. found that multiple SDOHs often cluster together in the same individual, playing a synergistic role in increasing an individual's risk of death from cancer (Pinheiro et al., 2022). Alternatively, education may also operate through modifiable health behaviors (Hahn & Truman, 2015; Zajacova & Lawrence, 2018), such as smoking (Siegel et al., 2021), alcohol use (Kunzmann et al., 2018), and inadequate physical activity (Cormie et al., 2017), which are associated with increased cancer mortality. Importantly, evidence from a systematic review suggests that these risk factors, especially alcohol misuse and smoking, often cluster together in the same individual, particularly among those with low education (Meader et al., 2016).

Although many studies have documented associations of patient education, individual SDOHs, and specific health behaviors with cancer mortality, there remain two important gaps in the literature. First, few studies have evaluated the effects of parental/caregiver education on cancer mortality in the United States. Most prior literature on this topic comes from Europe, where the health system is significantly different from that in the United States. Second, despite evidence that SDOHs and health behaviors represent two important domains that may mediate the association between educational attainment and cancer mortality, no study to our knowledge has evaluated which of these two domains is a stronger driver of the overall association between education and cancer mortality. In this study, we will evaluate the association between individual and parental/caregiver educational attainment and cancer mortality in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study cohort, a national United States cohort of Black and White participants. Furthermore, we will investigate whether the association between participant educational attainment and cancer mortality is mediated by the SDOH and health behaviors domains. A greater understanding of the pathways that produce poor health and lower survival among lower education individuals may provide useful insight to guide targeted interventions.

2. Materials and methods

2.1. REGARDS study population

Data were obtained from the REGARDS study, one of the largest population-based longitudinal studies of Black and White adults in the United States. The REGARDS study has been previously described in detail (Howard et al., 2005). Briefly, REGARDS enrolled 30,239 participants aged 45 years and older at baseline. The intention of the study was to examine contributing factors associated with the excess stroke mortality observed in the Southeastern United States and among Black adults. Therefore, 30% of participants were recruited from the "Stroke Belt" (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee), 20% from the "Stroke Buckle" (a region of the "Stroke Belt" in the coastal plains of Georgia, North Carolina, and South Carolina with particularly high stroke burden), and the remaining from other states. Recruitment occurred between January 2003 and October 2007 and follow-up is ongoing at 6-month intervals. Participants completed a computer-assisted telephone interview to collect information covering socio-demographic characteristics, health behaviors, and medical history. During a subsequent in-home examination conducted 4–6 weeks later, physical measurements, blood, and urine samples were collected. In 2011–2012, the Childhood and Family Life Questionnaire, a self-administered survey covering aspects of childhood socioeconomic status, was mailed to all active participants (N = 20,620) for completion (Martin et al., 2021). The Institutional Review Boards of all participating institutions approved the study, and all participants provided written informed consent.

2.2. Study cohort

Of the 30,239 participants, 56 had data anomalies, and 6 participants had a missing baseline survey date and were excluded due to an inability to determine length of follow-up. This resulted in 30,177 participants for inclusion in the main analysis. Of the 13,210 participants who returned the Childhood and Family Life Questions Survey, from which data on parental education was obtained, 1 participant had a missing baseline survey date, yielding 13,209 participants for our analysis of parental education.

2.3. Exposure – education

Educational attainment was self-reported on the baseline REGARDS survey. Study participants were categorized as having "high" or "low" educational attainment, consistent with previous research (Barcelo et al., 2021; Galea et al., 2011) where "high" education was high school graduate or greater and "low" education was less than high school. As noted by Barcelo et al. (2021), national studies (Rogers et al., 2010, 2013) have shown that those with less than 12 years of education experience the highest all-cause mortality rates in the United States, suggesting that high school completion represents a critical threshold for mortality risk. Among those included in the Childhood and Family Life Questionnaire cohort, the education levels of the participants' male and female caregivers (abbreviated mother and father herein) were similarly dichotomized. We determined life-course education for each participant relative to their mother and father: stable high (high participant education and high parental education), increasing (high participant education and low parental education), decreasing (low participant education and high parental education) or stable low (low participant education and low parental education).

2.4. Outcome – cancer mortality

All REGARDS participants were contacted to determine vital status at 6 month intervals. Deaths were also determined from medical records, based on reports from participants' proxies, and linkage with the Social Security Death Index and the National Death Index. Final cause of death was defined after adjudication by the REGARDS clinical investigators using all available information (Halanych et al., 2011). We determined time to cancer death as the number of days from the baseline REGARDS survey to the date of death.

2.5. Social determinants of health

Consistent with prior studies utilizing the REGARDS dataset (Pinheiro et al., 2022; Reshetnyak et al., 2020; Sterling et al., 2020), we incorporated the Healthy People 2030 framework of SDOH (HealthyPeople2030). We considered the following 6 unfavorable binary SDOHs: household income <$35,000; lacking health insurance; living in a zip code with >25% of the population below the poverty line; living in a state with poor public health infrastructure; living in a partial or complete health professional shortage area (HPSA) (Brown et al., 2011); and social isolation. Income, insurance status, and social isolation (not seeing friends or family members at least once per month) were determined from the REGARDS baseline survey. States with poor public health infrastructure were identified using data from America's Health Ranking; these states included Louisiana, New Mexico, Mississippi,

Nevada, South Carolina, Florida, Arkansas, Texas, and Tennessee, which were in the lowest decile >80% of the decade before REGARDS enrollment (1993–2002) (United Health Foundation). Zip code poverty level was obtained from the 2005–2009 American Community Survey data (American Community Survey 5, 2009). These SDOH measures are shown in relation to the Healthy People 2030 framework in Fig. 1.

2.6. Health behaviors

We considered the following 3 binary health behaviors: smoking (at least 100 cigarettes smoked in lifetime); alcohol use (heavy drinking based on sex-specific National Institute on Drug Abuse cut points; 7+ drinks/week for women and 14+ drinks/week for men); and failure to meet recommendations for physical activity (enough activity to work up a sweat on less than 4 days of the week). These data were collected at baseline. The included health behavior risk factors have been highlighted by the American Cancer Society as key contributors to the cancer burden in the United States (Rock et al., 2020). The smoking definition was selected to reflect lifetime increased disease risk (Taghizadeh et al., 2016), and the physical activity definition was aimed at capturing adherence to World Health Organization recommendations (Bull et al., 2020) of 150 min of weekly moderate intensity activity.

2.7. Covariates

Study covariates included a variety of demographic variables and medical conditions at baseline. Demographic covariates included: age (continuous); sex (male/female); race (White/Black); marital status (married, divorced, single, widowed, or other); and region (Stroke Belt, Stroke Buckle, or other). Medical conditions included: obesity (BMI >30 kg/m^2); hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or self-reported current medication use to control blood pressure), dyslipidemia (total cholesterol ≥240 mg/dL or LDL ≥160 mg/dL or HDL ≤40 mg/dL or self-reported use of lipid lowering medication), diabetes (fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL or use of pills or insulin to lower blood sugar), history of heart disease (self-reported myocardial infarction, coronary artery bypass graft, bypass, angioplasty or stenting, or evidence of myocardial infarction via electrocardiogram), and history of stroke (self-reported). We derived a health condition summary variable by summing the number of conditions present for each participant and creating categories (0, 1, 2, 3+). This method has been shown to predict mortality risk similarly to other measures such as the Charlson comorbidity index (Perkins et al., 2004).

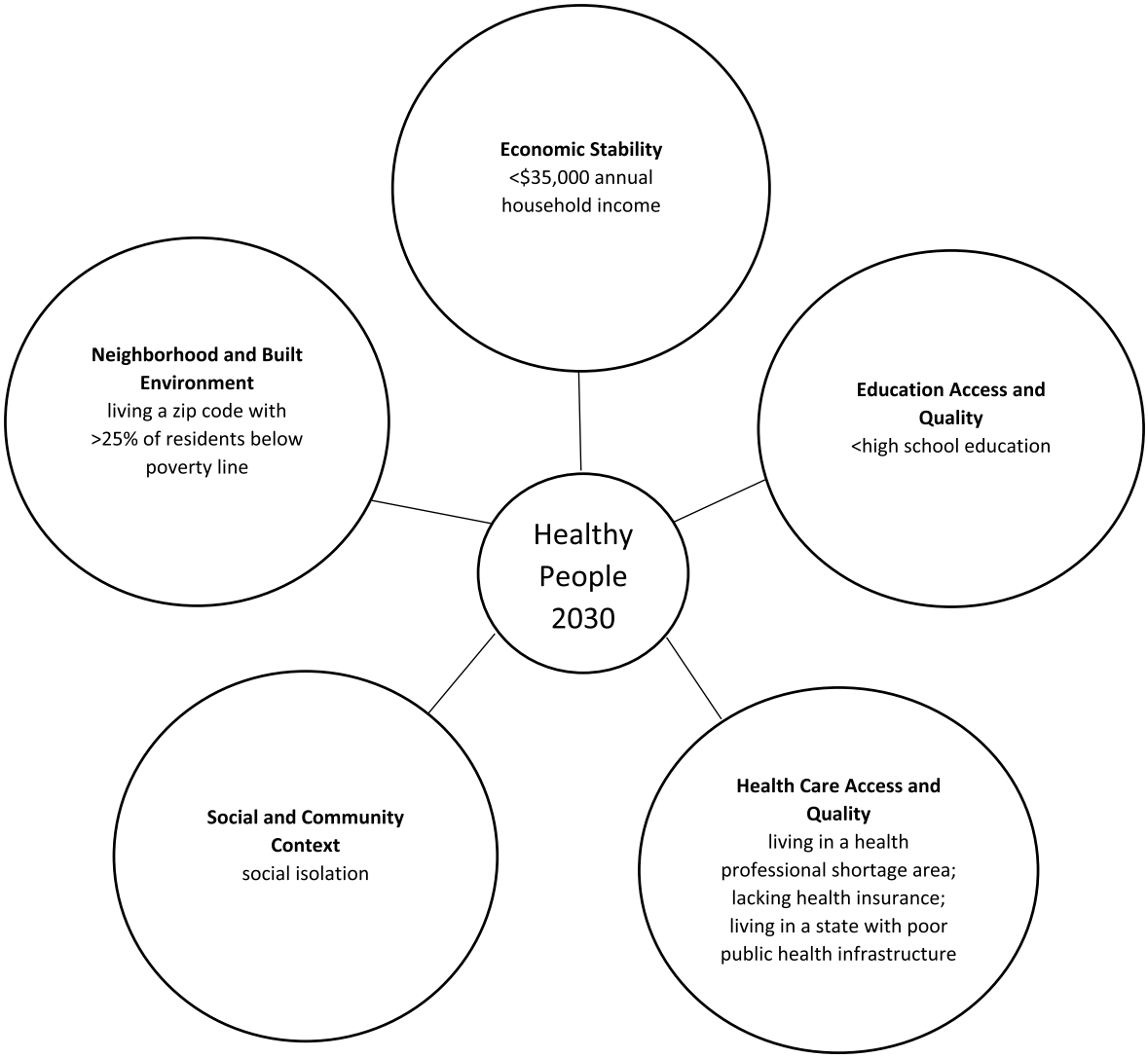

Fig. 1. Healthy People 2030 framework with measured social determinants of health (SDOH).

2.8. Statistical analysis

We performed multiple imputation by chained equations (Van Buuren & Oudshoorn, 1999) on variables that were missing in our main analysis. Data was not missing completely at random (MCAR); annual household income had the largest percentage of missing values (12%), with patients with lower educational attainment more likely to have missing values for income. All other variables had less than 5% missing. For the parental education variables, values were not imputed, and a missing category was maintained. For imputed variables, we assume data was missing at random (MAR) given observed data.

We used descriptive statistics to present the distribution (proportions) of baseline participants' characteristics by participant educational attainment, and among those included in the Childhood and Family Life Questionnaire cohort, by mother's educational attainment and father's educational attainment. We described participant education, parental education, and life-course education by race. We used univariable and multivariable cause-specific Cox proportional hazards models (Cox DRJJotRSSSB, 1972) to determine associations between the education variables (participant and parental educational attainment) and cancer mortality; the regression framework for the models can be expressed simply as the relative hazard of cancer mortality given the participant educational attainment and additional covariates $\left(\frac{h(t)}{h0(t)} = \exp(b1 * Education + b2 * X2 \ldots + bp * Xp)\right)$. Multivariable models were adjusted for two sets of covariates: Model 1 included sociodemographic characteristics only (age, sex, race, marital status, and region); and Model 2 included sociodemographic characteristics and patient health conditions (summary variable). Models for participant education were stratified by race to address violations of the proportional hazards assumption. The same modeling approach was used for the Childhood SES sub-cohort, with the primary exposure variables of interest being maternal and paternal education instead of participant education.

We evaluated within-domain associations between the 6 SDOH variables and 3 health behavior variables using univariable logistic regression models (Supplemental Tables 1a-b). Because we found strong correlations, we used principal components analysis (PCA) to generate single factor scores representing each domain (with higher scores representing more adverse conditions). Scree plots for each domain are shown in Fig. 2; these plots display the eigenvalues for each factor, which are the absolute values of the variance explained by each factor. Factor loadings are included in Supplemental Tables 2a-b. Using MPlus version 8 (Muthén & Muthén, 1998–2017), we used a structural equation modeling approach to fit cause-specific continuous time survival models testing potential mediation of participant education on cancer-specific mortality by each of the following variables: 1) SDOH domain score; and 2) health behaviors domain score. All models were stratified by race, adjusted for socio-demographic characteristics and health conditions, and included a mediation path from education to the mediating variable (SDOH domain score or health behavior score) to cancer mortality. We estimated direct, indirect, and total effects of participant education on cancer mortality with mediation by the health behavior score and the SDOH domain score separately; direct effects are calculated as the effect of participant education on the risk of cancer mortality without any additional effect occurring via the mediator, and the indirect effect is the effect of education on cancer mortality that acts through education's effect on the mediator only. The total effect of education on risk of cancer mortality is comprised of both the direct and indirect effects. To enable comparison with prior work in REGARDS (Pinheiro et al., 2022), we conducted sensitivity analyses in which we created count variables (0, 1, 2, etc.) for the SDOH and health behavior domains and evaluated mediation effects using these variables. Our findings were consistent using both methods (counts and PCA scores); therefore, we presented the main results using PCA-derived scores. Mediation analyses were not conducted for parental education, as cause-specific Cox proportional hazard models indicated no significant associations with cancer mortality. All analyses were conducted in SAS version 9.4 (Version 9, 2013) or MPlus version 8.

3. Results

3.1. Cohort characteristics

Among the 30,177 participants included in this analysis, the mean age at baseline was 64.8 years, 58.5% of participants were White, and 44.9% were male (Table 1). Those without a high school degree were older than those who had graduated high school (68.2 vs. 64.4 years). In total, 3798 participants (12.6%) had less than a high school degree. Those without a high school degree were more likely to have an income <$35,000 (87.7% vs. 43.6%), be uninsured (9.9% vs. 6.2%), live in a zip code with >25% of the population below the poverty line (35.1% vs. 17.7%), live in a state with poor public health infrastructure (40.7% vs. 34.3%), live in a partial or complete HPSA (44.7% vs. 41.9%), and be socially isolated (5.6% vs. 4.7%) (Table 1). High school graduates were more likely to be heavy alcohol drinkers (4.2% vs. 2.5%), and those without a high school degree were more likely to have smoked at least 100 cigarettes in their lifetimes (61.5% vs. 53.8%). Cohort characteristics by mother's education and father's education (N = 13,209) are shown in Supplemental Tables 3a-b.

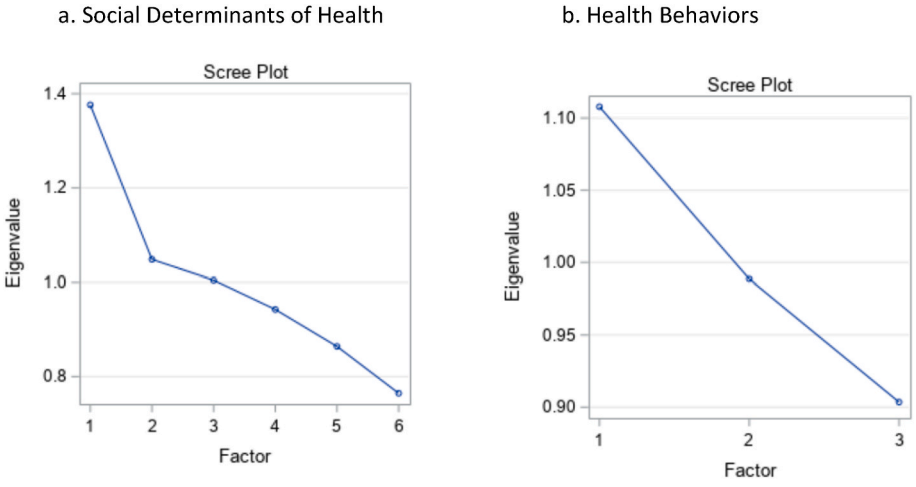

Fig. 2. Scree plots for results of principal components analysis; the plotted eigenvalues represent the absolute value of variance explained by each factor. a. Social Determinants of Health b. Health Behaviors.

Table 1
Sociodemographic characteristics, health conditions, and social determinants of health of REGARDS participants by participant education level.

	Total	Less Than High School Degree	High School Degree +
	N = 30177	N (%) = 3798 (12.6)	N (%) = 26379 (87.4)
Sociodemographic			
Age (mean, SD)	64.8 (9.4)	68.2 (9.2)	64.4 (9.4)
Race			
White	17666 (58.5)	1295 (34.1)	16371 (62.1)
Black	12511 (41.5)	2503 (65.9)	10008 (37.9)
Marital Status			
Married	17709 (58.7)	1713 (45.1)	15996 (60.6)
Divorced	4417 (14.6)	522 (13.7)	3895 (14.8)
Other	728 (2.4)	186 (4.9)	542 (2.1)
Single	1606 (5.3)	191 (5.0)	1415 (5.4)
Widowed	5717 (18.9)	1186 (31.2)	4531 (17.2)
Sex			
Male	13549 (44.9)	1560 (41.1)	11989 (45.4)
Female	16628 (55.1)	2238 (58.9)	14390 (54.6)
Region			
Stroke Belt	10444 (34.6)	1486 (39.1)	8958 (34.0)
Stroke Buckle	6305 (20.9)	870 (22.9)	5435 (20.6)
Other	13428 (44.5)	1442 (38.0)	11986 (45.4)
Health Conditions at Baseline			
[a]Obesity	11607 (38.5)	1709 (45.0)	9898 (37.5)
[b]Hypertension	17888 (59.3)	2750 (72.4)	15138 (57.4)
[c]Dyslipidemia	17871 (59.2)	2389 (62.9)	15482 (58.7)
[d]Diabetes	6669 (22.1)	1327 (34.9)	5341 (20.2)
[e]History of Heart Disease	5454 (18.1)	931 (24.5)	4523 (17.1)
[f]History of Stroke	1939 (6.4)	455 (12.0)	1483 (5.6)
Social Determinants of Health			
Income <$35,000	14842 (49.2)	3332 (87.7)	11510 (43.6)
No Health Insurance	2008 (6.7)	376 (9.9)	1632 (6.2)
Zip Code >25% Population Below Poverty Line	5998 (19.9)	1335 (35.1)	4663 (17.7)
Living in a State with Poor Health Infrastructure	10588 (35.1)	1547 (40.7)	9041 (34.3)
Living in a Partial or Complete Health Professional Shortage Area (HPSA)	12763 (42.3)	1698 (44.7)	11065 (41.9)
Social Isolation	1448 (4.8)	214 (5.6)	1233 (4.7)
Health Behaviors			
Alcohol (Heavy Drinking)	1211 (4.0)	96 (2.5)	1115 (4.2)
Physical Activity (<4 days/week)	21248 (70.4)	2749 (72.4)	18499 (70.1)
100 + Cigarettes Smoked in Lifetime	16524 (54.8)	2335 (61.5)	14189 (53.8)

[a] BMI ≥30 kg/m^2.
[b] Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or self-reported current medication use to control blood pressure.
[c] Total cholesterol ≥240 mg/dL or LDL ≥160 mg/dL or HDL ≤40 mg/dL or self-reported use of lipid lowering medication.
[d] Fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL or use of pills or insulin to lower blood sugar.
[e] Self-reported physician diagnosis of myocardial infarction (MI), coronary artery bypass graft, bypass, angioplasty, or stenting, or evidence of MI via electrocardiogram.
[f] Self-reported physician diagnosis of history of stroke.

Only 7.3% of White participants had less than a high school education compared with 20.0% of Black participants (Fig. 3). In the Childhood and Family Life Questionnaire cohort (N = 13,209), 37.4% of mothers and 41.5% of fathers among White participants had less than a high school education, whereas 54.9% of mothers and 51.8% of fathers had not completed high school among Black participants. Among White participants, 6.9% of mothers and 10.4% of fathers had missing parental education; among Black participants, 14.7% of mothers and 26.5% of fathers had missing parental education. Additionally, 55.0% of White participants and 29.3% of Black participants had stable high life-course education with respect to their mothers; 34.6% of White participants and 48.6% of Black participants had increasing life-course education. With respect to their fathers, 47.6% of White participants and 21.1% of Black participants had stable high life-course education; 39.1% of White participants and 46.5% of Black participants had increasing life-course education.

3.2. Education and cancer mortality

For our analysis of participant education, the median follow-up time in our sample was 10.7 years (standard deviation: 5.0 years). Over this duration, 2249 cancer-related deaths occurred. In Cox proportional hazards models assessing the risk of cancer mortality among White participants, those without a high school education experienced 84% higher risk of death than high school graduates (unadjusted hazard ratio (HR): 1.84; 95% confidence interval (CI): 1.54, 2.20) (Table 2). This association remained significant but was attenuated after adjusting for socio-demographic characteristics and health conditions (HR: 1.47; 95% CI: 1.23, 1.76). Associations among Black participants were consistent with estimates among White participants (fully adjusted HR: 1.54; 95% CI: 1.33, 1.79). For our analysis of parental education (N = 13,209), median follow-up time in our sample was 14.0 years (standard deviation: 2.7 years); there were 507 cancer-related deaths. No significant associations were observed for parental education in fully adjusted models (mother HR: 0.90; 95% CI: 0.74, 1.09 and father HR: 0.82; 95% CI: 0.68, 1.00) (Table 2).

3.3. Mediation analysis

We observed differences in the SDOH (range: -1.25 to 3.62) and health behavior (range: -1.02 to 4.21) domain scores by educational attainment. Participants who did not complete high school had higher SDOH and health behavior domain scores than high school graduates, with higher scores indicating more adverse conditions (Supplemental Table 4). In the mediation analysis, results were consistent by race. For the SDOH domain score, there was evidence of a small mediation effect (White total effect HR: 1.25; 95% CI: 1.18, 1.33, indirect effect HR: 1.04; 95% CI: 1.03, 1.05, direct effect HR: 1.21; 95% CI: 1.14, 1.28 and Black total effect HR: 1.24; 95% CI: 1.18, 1.29, indirect effect HR: 1.04; 95% CI: 1.03, 1.05, direct effect HR: 1.19; 95% CI: 1.14, 1.24) (Table 3, Fig. 4). There was no evidence of mediation by the health behaviors score. Results from sensitivity analyses evaluating the SDOH and health behavior count variables were consistent (Supplemental Table 5).

4. Discussion

In this study from a national cohort of Black and White adults in the United States, we found that individuals without a high school degree had a significantly higher risk of cancer mortality than high school

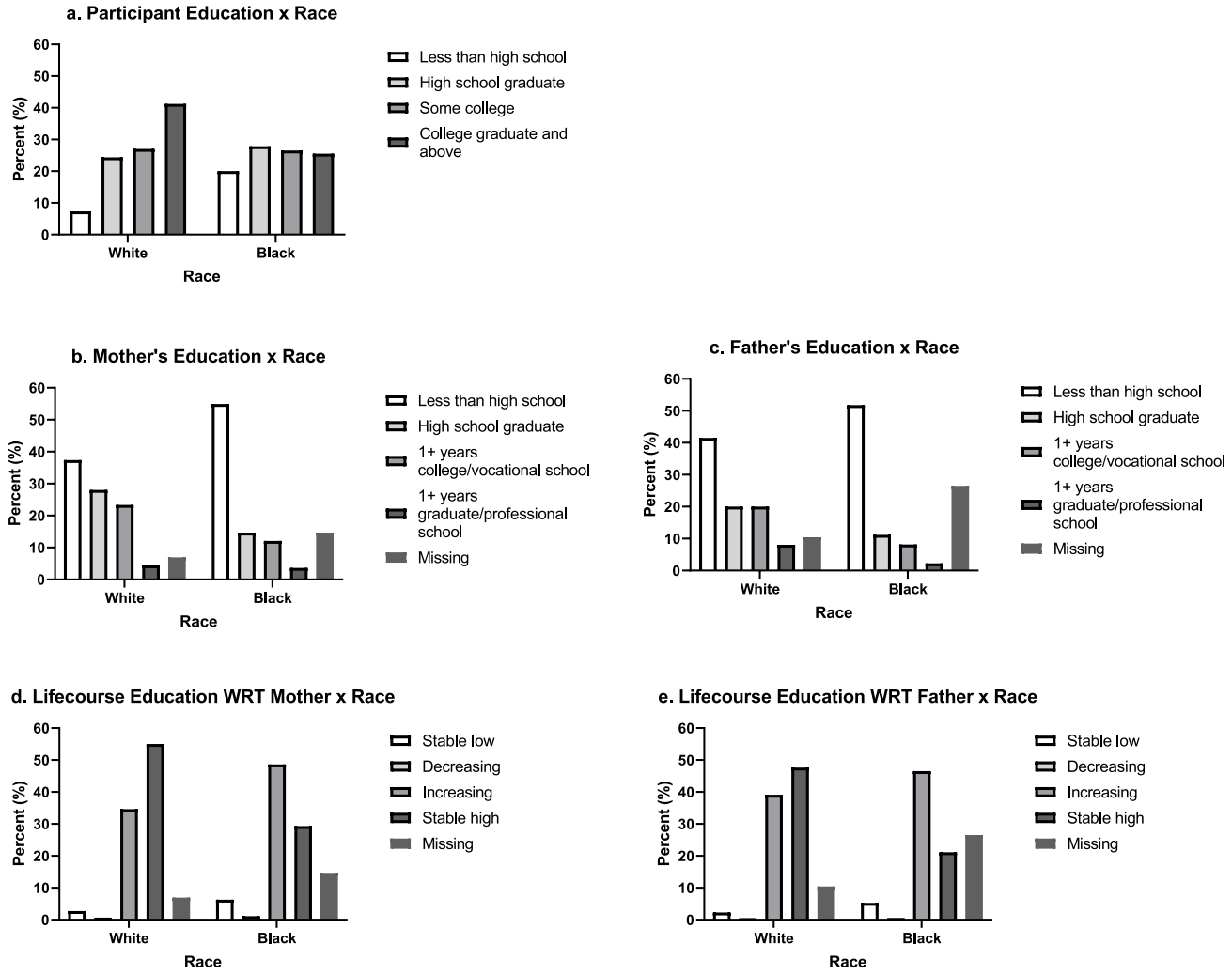

Fig. 3. Participant, parental and life-course education. For the life-course education variables, participant and parental education were each defined: high (high school graduate or greater) or low (less than high school). Life-course designations were then specified as: stable low (low parental and participant education); decreasing (high parental and low participant education); increasing (low parental and high participant education) or stable high (high parental and participant education). Missing values for the life-course education variables are due to missing data for parental education. WRT = with respect to.

graduates. However, there were no significant associations between parental education and participant cancer mortality. The association between participant education and cancer mortality was partially mediated by the SDOHs but not health behaviors. These findings suggest that strategies addressing SDOHs – such as insurance status and public health infrastructure – may help to improve cancer mortality among individuals with low education.

Our results indicating that low education is associated with a higher risk of cancer mortality are consistent with several previous studies in the United States (Albano et al., 2007; Barcelo et al., 2021; Coughlin, 2020). Barcelo et al. used United States National Center for Health Statistics death certificate data on 8.2 million people to evaluate the influence of education on cancer mortality. They found that age-adjusted cancer mortality rates increased between 1989 and 2018 among those with an education of less than 12 years, while they decreased among those with 12 or more years of education, indicating widening cancer mortality disparities by educational attainment (Barcelo et al., 2021). These alarming results suggest that individuals with low educational attainment may not be benefiting from scientific advances in cancer care, and underscore the urgent need for interventions aimed at increasing access to cancer prevention, screening, and quality treatment to reduce the mortality burden.

Our null results for mother's and father's education (i.e., proxy for early-life socioeconomic position) are consistent with findings from a review by Vohra et al. that noted no significant association between head of household's occupation and total cancer mortality in 9 of 11 studies evaluated (Vohra et al., 2016). However, our findings are contrary to past studies indicating an association between early-life socioeconomic position and cancer mortality. Results from Pudrovska and Anikputa showed that father's education was negatively related to breast cancer mortality among non-Hispanic White women in the United States (Pudrovska & Anikputa, 2012). Additionally, in a prior study of Nigerian women, we found that participants with highly educated fathers were 60% less likely to have high-grade breast cancer, which is prognostic of poorer survival, though the Nigerian context may not be representative of the health system in the United States (Gupta et al., 2021). These mixed findings may be related to heterogeneity in the association between parental educational attainment and cancer mortality by cancer type. For example, among studies that categorized cancer outcomes as either smoking or non-smoking related, Vohra et al.

Table 2
Cox cause-specific hazard ratios for cancer-specific death.

	Unadjusted HR (95% CI)	Demographics[a] HR (95% CI)	Fully-Adjusted[b] HR (95% CI)
Full Cohort (N = 30177)			
Participant Education (White) (N = 17666)			
HS+	Ref.	Ref.	Ref.
<HS	1.84 (1.54, 2.20)	1.52 (1.27, 1.82)	1.47 (1.23, 1.76)
Participant Education (Black) (N = 12511)			
HS+	Ref.	Ref.	Ref.
<HS	1.90 (1.64, 2.19)	1.54 (1.33, 1.79)	1.54 (1.33, 1.79)
Childhood SES Cohort (N = 13209)			
Mother's Education			
HS+	Ref.	Ref.	Ref.
<HS	1.05 (0.87, 1.26)	0.91 (0.75, 1.10)	0.90 (0.74, 1.09)
Missing	1.46 (1.10, 1.94)	1.12 (0.83, 1.50)	1.10 (0.82, 1.48)
Father's Education			
HS+	Ref.	Ref.	Ref.
<HS	0.98 (0.81, 1.19)	0.84 (0.69, 1.02)	0.82 (0.68, 1.00)
Missing	1.25 (0.97, 1.60)	1.03 (0.79, 1.34)	1.01 (0.78, 1.32)

[a] Adjusted for age, sex, race (not included in race-stratified models), marital status, and region.
[b] Additionally adjusted for health conditions (sum of obesity, hypertension, dyslipidemia, diabetes, heart disease, and stroke).

Table 3
Mediation analysis for the association between education and cancer-specific death by social determinants of health (SDOH) and health behavior domain scores.

	White Participants		Black Participants	
	HR (95% CI)[a]	Proportion Mediated	HR (95% CI)[a]	Proportion Mediated
Mediation- SODH Domain Score				
Total Effect		16%		17%
HS Graduate	Ref.		Ref.	
Not HS Graduate	1.25 (1.18, 1.33)		1.24 (1.18, 1.29)	
Indirect Effect Mediated via SODH Score				
HS Graduate	Ref.		Ref.	
Not HS Graduate	1.04 (1.03, 1.05)		1.04 (1.03, 1.05)	
Direct Effect				
HS Graduate	Ref.		Ref.	
Not HS Graduate	1.21 (1.14, 1.28)		1.19 (1.14, 1.24)	
Mediation- Health Behavior Domain Score				
Total Effect		0%		0%
HS Graduate	Ref.		Ref.	
Not HS Graduate	1.24 (1.17, 1.32)		1.24 (1.18, 1.29)	
Indirect Effect Mediated via Behavior Score				
HS Graduate	Ref.		Ref.	
Not HS Graduate	1.00 (1.00, 1.00)		1.00 (1.00, 1.00)	
Direct Effect				
HS Graduate	Ref.		Ref.	
Not HS Graduate	1.24 (1.17, 1.32)		1.24 (1.18, 1.29)	

HS = high school.
[a] Adjusted for age, sex, marital status, region, and health conditions (sum of obesity, hypertension, dyslipidemia, diabetes, heart disease, and stroke).

found that only the smoking-related cancers were related to early-life socioeconomic position (Vohra et al., 2016). However, we were unable to evaluate the association between parental education attainment and cancer mortality separately for different cancer types due to limited

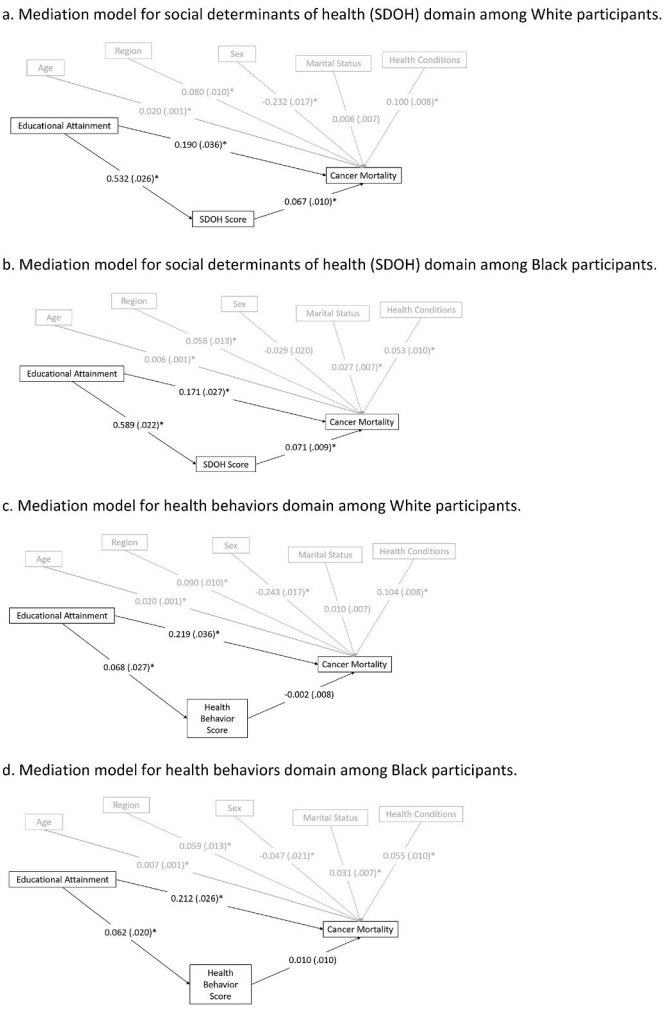

Fig. 4. Structural equation models for mediation analysis of the association between education and cancer mortality. Numbers represent estimates of the associations between each pair of variables (standard error). * indicates $p < 0.05$. a. Mediation model for social determinants of health (SDOH) domain among White participants. b. Mediation model for social determinants of health (SDOH) domain among Black participants. c. Mediation model for health behaviors domain among White participants. d. Mediation model for health behaviors domain among Black participants.

cancer death events in our subsample with parental education data available.

We observed a modest mediation effect for the SDOH domain score, suggesting that education may partially influence cancer mortality via variables such as income, zip code poverty level, and regional access to quality healthcare resources. Previous research has indicated associations between education and individual SDOHs, and associations between individual SDOHs and cancer mortality. For example, there are consistent associations of low educational attainment with low income (Mirowsky & Ross, 2017), lack of insurance (Kaplan et al., 2017), and receiving cancer care that is not concordant with guideline recommendations (Farrow et al., 2020). In turn, having a low income (Singh & Jemal, 2017), receiving care at lower volume healthcare facilities (Bristow et al., 2014; Greenup et al., 2018), living in an impoverished area (Singh & Jemal, 2017; O'Connor et al., 2018), and lacking health insurance (Cole et al., 2019; Mohamed et al., 2020) are all associated with increased cancer mortality. The fact that the SDOH domain only partially mediated the association between educational attainment and cancer mortality in our study is consistent with previous research evaluating income as a mediator of this association. For example, in a

study of the National Health and Nutritional Examination Survey (NHANES III), Rogers et al. showed that controlling for income attenuates the association between education and cancer mortality but does not fully explain it (Rogers et al., 2013). Kaplan et al. found similar results in the REGARDS dataset for all-cause mortality (Kaplan et al., 2015). However, beyond income, few studies have specifically evaluated the mediating effects of elements of the SDOH domain. Other studies on this topic adjust for a wide range of covariates simultaneously (Kaplan et al., 2017), making it difficult to tease out the differential effects of this domain from other mediation pathways. There is a need for further research that comprehensively evaluates the individual and joint mediation effects of elements of the SDOH domain.

Our finding that there was no mediation effect through the health behaviors domain was surprising. Inconsistent with our results, multiple previous studies have found significant partial mediation effects through behavioral risk factors, with the strongest effects observed for smoking status (Kilander et al., 2001; Nordahl et al., 2014). Nordahl et al. found that smoking mediated 29% of the observed association between education and cancer mortality among Danish men under 65; physical activity and alcohol intake mediated 1% and 6% of the association, respectively (Nordahl et al., 2014). Similarly, Kilander et al. found that controlling for smoking, physical activity, and dietary biomarkers attenuated the excess cancer mortality among men with lower education in Sweden (Kilander et al., 2001). While these prior studies adjusted for the covariates age and sex (Nordahl et al., 2014), and age only (Kilander et al., 2001), we adjusted for a much wider range of covariates, including broader socio-demographic characteristics and health history. Furthermore, differences in our findings may be due to setting; most past research on this topic has been conducted in European countries with starkly different health systems compared to the United States and has not included different racial groups. It is also worth noting that health behaviors in our study were captured at baseline, and therefore, our data do not account for changes in these behaviors over the follow-up period, which previous literature (Yoo et al., 2022) has shown to significantly alter cancer mortality risk.

Our results and those of previous studies indicate a persistent effect between educational attainment and cancer mortality after accounting for SDOHs and health behaviors. This suggests that education may act through pathways not captured in the current analysis. For instance, educational attainment may contribute to health knowledge, literacy, and confidence navigating the healthcare system (Hahn & Truman, 2015). In fact, a recent review found that educational attainment is the most important determinant of heath literacy, and that health literacy mediates the relationship between socioeconomic status and health status, quality of life, health behaviors, and use of preventive services (Stormacq et al., 2019). Health literacy may be particularly important in the context of cancer care, as patients are required to navigate complex diagnostic and treatment decisions while severely ill (Dumenci et al., 2014). Alternatively, educational attainment may influence an individual's working conditions, affecting their exposure to health hazards related to cancer incidence, and thus mortality (Hahn & Truman, 2015). Furthermore, although we evaluated the regional availability of healthcare resources as part of the SDOH domain, we were unable to explore their utilization. Patient decisions regarding care are multifactorial and complex, extending beyond the mere availability of healthcare to include aspects such as the patient-provider relationship and personal values and preferences (Pozzar & Berry, 2017). Future research that explores these additional pathways from educational attainment to cancer mortality may be beneficial in designing targeted interventions to improve cancer outcomes among individuals with low educational attainment. It will also be important for future research to disentangle the role of race in this association. A history of structural racism in the United States has produced significant racial disparities in access to socioeconomic resources (Merolla & Jackson, 2019), also reflected in our study, and historic patterns of poor interactions between medical centers and communities of color have sown mistrust that may affect care-seeking behaviors (Jaiswal & Halkitis, 2019).

Our study has some limitations. First, we were unable to determine cancer mortality by type of cancer. Previous research suggests that the influence of education on cancer mortality might vary by cancer type (Vohra et al., 2016). Second, several of our variables, including alcohol use and physical activity, were self-reported, introducing the potential for recall bias. Third, we also acknowledge that there are SDOHs and health behaviors that were not captured in our study, but that may play important roles as mediators of the association between educational attainment and cancer mortality (i.e., working conditions, dietary patterns, health care utilization, etc.). Likewise, different thresholds for the included measures (education, income, area-level poverty, etc.) may produce varying outcomes. Finally, we note that the proportion of participants with less than a high school degree in our sample (13%) was slightly lower than the national average reported by the United States Census Bureau in 2003 (15%), (Stoops, 2004) and therefore our sample may not be fully representative of the United States population. Still strengths of our study include the use of data from a large prospective cohort with a relatively long follow-up period, the ability to adjust for a variety of sociodemographic and clinical covariates, and the inclusion of parental education.

In conclusion, we found a strong, significant association between participant educational attainment and cancer mortality in the REGARDS study, and this association was mediated by the SDOHs. Future research exploring additional mediation pathways and interventions targeting these pathways is warranted. Efforts to target multiple SDOHs among individuals with low education may help to ameliorate socioeconomic disparities in cancer mortality.

CRediT authorship contribution statement

Anjali Gupta: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Lauren E. Wilson:** Methodology, Formal analysis, Writing – review & editing. **Laura C. Pinheiro:** Conceptualization, Writing – review & editing. **Amy H. Herring:** Conceptualization, Writing – review & editing. **Tyson Brown:** Conceptualization, Writing – review & editing. **Virginia J. Howard:** Data curation, Writing – review & editing. **Tomi F. Akinyemiju:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Wilson reports research funding paid to Duke University from AstraZeneca, outside the submitted work. All other authors declare no competing interests.

Data availability

Requests to access REGARDS data may be submitted at http://regardsstudy.org.

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institutions can be found at: https://www.uab.edu/soph/regardsstudy/.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2023.101546.

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