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Educational attainment, health locus of control and inflammation among cancer survivors in the Midlife in the United States (MIDUS) study

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ABSTRACT

The goal of this study was to investigate whether HLOC mediates the relationship between educational attainment and inflammatory proteins in cancer survivors. Data are from 298 cancer survivors (87.54% white; *M* age = 63.6; *M* survivorships = 15 years) who participated in the Biomarker protocol of Wave 2 and Refresher phases of the Midlife in the United States (MIDUS) study. Educational attainment was dichotomized (bachelor's degree or above versus lower). The two measures of HLOC were based on whether participants felt others had control over their health outcomes (external HLOC) or if they felt they were in control of their health outcomes (internal HLOC). We used C-reactive protein (CRP) and interleukin-6 (IL-6) as markers of inflammation. Mediation analyses for external and internal HLOC were tested separately. Mediation analyses were conducted using the PROCESS package in R (using 10 000 bootstrapped samples). Analyses were adjusted for age, sex, cohort, body mass index (BMI), smoking status, and race/ethnicity. In the fully adjusted model, educational attainment and external HLOC were significantly associated with CRP. Relative to those with bachelor's degrees, participants with lower educational attainment had elevated CRP (b = -0.25, SE = 0.11, 95% CI = [−0.47, −0.03]). Higher external HLOC was linked to increased CRP (b = 0.10, SE = 0.04, 95% CI = [0.01, 0.18]). The mediation analyses showed that a higher external HLOC was a significant path through which lower educational attainment was associated with elevated CRP (indirect effect = -0.05, bootstrapped SE = 0.02, 95% CI [bootstrapped] = [−0.10, −0.01]. Cancer survivors with lower educational attainment may tend to perceive that their health is outside of their control. These socioeconomic and psychosocial processes may drive an increase in the circulating levels of inflammatory signaling proteins known to be sensitive predictors of age-related chronic diseases.

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Background

Persistent health inequities based on socioeconomic status (SES) are a major public health concern in the United States and many other countries (Adler et al., 1994; Braveman et al., 2010). SES, or a group of valued resources, both material and social (income, educational attainment, social status), is a fundamental contributor to health and disease as higher SES is positively associated with the ability to avoid health risks more optimally and to minimize the adverse course following disease (Phelan et al., 2010). Differences in SES create disparities in health through biological, social, and psychological pathways (Matthews et al., 2010). Lower SES is often associated with a higher exposure to chronic stressors (e.g. chronic financial strain, chronic community pressures, and/or chronic environmental stressors) and less access to medical care and psychosocial resources (e.g. fewer social supports and less social capital). These factors contribute to physiological wear and tear and accelerated aging. Dysregulation of inflammatory physiology and weakened immune function is a major consequence of the physiological wear-and-tear associated with lower SES, more frequent exposure to stressors, and limited psychosocial resources. Collectively, they contribute to the development of age-related chronic diseases and premature mortality (Chiang et al., 2019; Mainous et al., 2024; Yegorov et al., 2020).

Educational attainment is one of the most important and widely used indicators of SES in health inequities research (Krieger et al., 1997). Educational attainment-related disparities in age-related morbidity and premature mortality are well documented (Balaj et al., 2024; Smith et al., 2015). Individuals with lower educational attainment tend to experience more exposure to chronic stressors and less access to psychosocial resources (Matthews et al., 2010). Further, research has documented robust evidence on the link between lower educational attainment and dysregulation of inflammatory physiology and weakened immune function due to physiological wear-and-tear associated with frequent exposure to stressors and limited psychosocial resources. In a recent meta-analysis, lower education was associated with elevated levels of inflammatory markers of disease risk (Muscatell et al., 2020). Thus, dysregulation in systemic inflammation is a critical biological pathway that can link lower educational attainment to morbidity and mortality.

Biopsychosocial factors of health disparities associated with educational attainment among cancer survivors

While the biopsychosocial factors associated with educational disparities in health have been extensively investigated among the general population, less is known regarding the importance of these biological and psychological factors of socioeconomic disparities on the health of cancer survivors. Relative to those with higher educational attainment, cancer survivors with lower educational backgrounds are more likely to have an impaired health-related quality of life (Mielck et al., 2014), greater risk for cardiovascular disease (Satti et al., 2023), and shorter duration of survivorship (Coughlin, 2019).

Cancer is typically a disease that increases with age with more than three-quarters of cancer survivors being 60 years and older (Tonorezos et al., 2024). Nevertheless, improvements in cancer treatments have led to a growing number of long-term cancer

survivors (Bluethmann et al., 2016). But cancer and cancer treatments accelerate biological aging among cancer survivors (Wang et al., 2021), reduce overall physiological integrity, and precipitate the risk for other chronic health conditions (Elliott et al., 2011), including diabetes, cardiovascular disease, and Alzheimer's disease and related dementias (ADRD) – known as secondary chronic conditions (Ording et al., 2020; Ragni et al., 2021). These secondary chronic conditions among cancer survivors can lead to a compromised functional capability, a lower quality of life, and foreshortened healthspan and lifespan. Cancer survivors from lower educational backgrounds are at greater risk of developing secondary chronic co-morbid conditions (Ogle et al., 2000).

Low-grade chronic inflammation, an indicator of inflammatory physiology and weakened immune function, has been utilized as a bioindicator of accelerated aging among cancer survivors (Teissier et al., 2022). Chronic low-grade inflammation among cancer survivors is associated with an elevated risk of various age-related diseases, as noted above, including cardiovascular disease, metabolic dysregulation, and progressive cognitive decline (Carroll et al., 2023; Koene et al., 2016; Pati et al., 2023). Emerging evidence has shown that lower SES among cancer survivors, including lower educational attainment, significantly contributes to elevated inflammation (Blaes et al., 2023; Pageot et al., 2022). Thus, cancer survivors from lower educational backgrounds are more likely to experience accelerated aging and age-related chronic diseases.

Little is known about how psychosocial factors contribute to the association between lower SES and elevated inflammation among cancer survivors. An emerging body of research involving the general population has examined the role of perceived control or locus of control as an important psychosocial resource that may mediate this association. Lower SES, including lower educational attainment, is generally associated with a lower internal locus of control and a higher external locus of control (Zahodne et al., 2019). Sociological perspective on SES and locus of control posits that formal education is an important social context where a sense of control is developed (Mirowsky & Ross, 2007; Shieman & Plickert, 2008). Studies have documented that locus of control is higher with the addition of schooling (Mirowsky & Ross, 2007; Shieman & Plickert, 2008). On the other hand, lower educational attainment is associated with the lack of internal control and the belief that external factors have a stronger control in life outcomes (Mitchell et al., 2018). The lack of internal control and higher perception of external constraints may be an important psychosocial mechanism of how lower educational attainment contributes to worse health. External factors may play a more substantial role in health because they can be the individual-level manifestation of social and structural factors of health and well-being throughout the life course (e.g. higher levels of discrimination) (Zahodne et al., 2019). Further, emerging evidence shows that locus of control, especially higher external locus of control, is associated with elevated inflammation (Magin et al., 2024; Zahodne et al., 2019). How the locus of control contributes to the association between lower educational attainment and inflammation among cancer survivors is not known.

There is evidence that psychosocial factors play a critical mediating role in the eductaion-health relationship (Matthews et al., 2010), and that a lower sense of control is an essential psychosocial factor associated with both low educational attainment (Zahodne et al., 2019) and elevated inflammatory activity (Poortinga et al., 2008; Zahodne et al., 2019). One study has shown that perceived control

mediates the effects of lower SES, including lower educational attainment, and chronic stress (Mooney et al., 2018). Therefore, locus of control may be an important psychosocial factor that mediates the link between lower educational attainment and elevated inflammation.

Specifically, health locus of control (HLOC) is an important point of investigation because it measures how many individuals perceive control over their health outcomes, and it is a strong predictor of individuals' health behaviors (Lindström et al., 2022). Similar to the general perceived control, health locus of control also includes both internal (e.g. belief that one's behavior is linked to health) and external domains (e.g. one's doctor and access to medical care) (Wallston, 2020). Previous studies have documented the role of educational attainment in shaping HLOC, in which lower educational attainment is generally associated with lower internal HLOC and higher external HLOC (Grotz et al., 2011; Jacobs-Lawson et al., 2011). The HLOC of cancer patients and survivors is likely to change dynamically throughout the cancer experience (Li et al., 2023). One study among breast cancer patients found elevated internal HLOC at earlier stages of cancer diagnosis (I and II), and higher external HLOC at later stages (III and IV) of diagnosis (Rehman, 2022). However, there is a lack of empirical evidence on the significant associations between health locus of control and inflammation, either in the general population or among cancer survivors. Previous studies though have documented a significant association between HLOC and other biological indicators of chronic diseases, with robust evidence of socioeconomic disparities, including markers of insulin resistance (Eriksson et al., 2023) and allostatic load (Zilioli et al., 2015). Thus, we hypothesized that HLOC will be an important psychosocial factor for inflammation, especially among cancer survivors. Furthermore, HLOC would be an important psychosocial pathway through which lower educational attainment would be associated with elevated inflammation.

The current study

In summary, psychosocial factors, including health locus of control, may play a significant role in mediating the socioeconomic disparities in health among cancer survivors. This study examined the association among educational attainment, internal and external health locus of control, and the circulating levels of two inflammatory proteins among cancer survivors. We hypothesized that health locus of control would mediate the association between lower educational attainment and elevated inflammatory activity among cancer survivors. This analysis specifically tested the following hypotheses:

H1: Lower educational attainment is associated with elevated levels of CRP and IL-6.

H2: Lower internal HLOC and higher external HLOC are associated with elevated inflammatory activity

H3: Lower internal HLOC and higher external HLOC mediate the association between lower educational attainment and elevated levels of inflammatory proteins in circulation.

Methods

Data and participants

Data for these analyses are from the Midlife in the United States (MIDUS) study, a national cohort study on the health and well-being of middle-aged and older American adults. Extensive descriptions of the study are provided elsewhere (Barry, 2014; Brim et al., 2005). Here, we provided important details of the MIDUS study relevant to the current analysis. The MIDUS study started in 1995–1996 (MIDUS 1), where 7,108 adults (ages 25 to 74) from across the contiguous U.S.A. were recruited through random digit dialing and completed baseline interviews over the phone and self-administered questionnaires (SAQs). A decade later, 4,963 participants completed the first longitudinal follow-up (MIDUS 2; 2004–2006). To increase racial diversity among the study participants, the MIDUS 2 study recruited an oversample that included mostly Black adults ($N = 592$, ~94% Black) from Milwaukee County, Wisconsin, as part of the MIDUS 2 Milwaukee study (2005–2006). Also introduced during the MIDUS 2 was biospecimen collection, known as the MIDUS 2 Biomarker project (from 2004–2009). Of all the MIDUS 2 participants, 1,255 completed the MIDUS 2 Biomarker protocol.

In 2012–2016, a new national sample ($N = 3,577$), matching the sociodemographic characteristics of participants in MIDUS 1, was recruited to be part of the MIDUS Refresher study (MIDUS R). The main goal of the new phase was to replenish the number of younger participants to correspond to the original MIDUS sample as well as to investigate the impact of the economic recession in 2007–2008 on the health and well-being of American adults. MIDUS R also included an oversampling of Black adults (~91% Black) recruited from Milwaukee County, Wisconsin, known as the MIDUS R Milwaukee ($N = 508$; 2011–2013). Finally, the MIDUS R study also included biological specimen collection similar to the prior Biomarker protocol. A subset of the MIDUS R national participants and the Milwaukee oversample completed the MIDUS R Biomarker study ($N = 863$; 2012–2016).

Biomarker assessment protocol

In both MIDUS 2 and MIDUS R Biomarker Projects, participants stayed overnight at a clinical research unit (CRU). Participants attended the CRU site that imposed the least travel burden on one of three CRUs in Madison, WI, Washington, DC, or Los Angeles, CA. Fasted blood samples were collected on the morning of the second day at the facility to determine inflammation biomarkers. Blood samples were collected by trained phlebotomists and spun in refrigerated centrifuges. Frozen sera were stored in ultracold freezers until analyzed using standardized procedures. During the MIDUS 2 and MIDUS R Biomarker studies, participants were also asked if they had ever been diagnosed with cancer. Out of 2,118 participants, 298 reported that they had a cancer diagnosis (i.e. cancer survivors). A similar question was asked as part of the MIDUS baseline survey, with additional questions regarding age at diagnosis and type of cancer (208 participants provided this information).

Analytic sample

The current analyses utilized data from 301 cancer survivors who completed the survey and the biomarker study protocol in MIDUS 2 and MIDUS R. Among the participants who provided information regarding cancer types ($n = 207$), they include (Table 1): skin ($n = 70$), breast (37), and prostate (21), cervical (17), uterine (11), colon (8), lymphoma/leukemia (5), lung (4), ovarian (3), and others (45). Among

Table 1. Descriptive statistics of demographic, socioeconomic, and health-related factors among cancer survivors in this study ($N = 301$).

Variables	Missing	*n* (%)	M (SD)	Range
Demographic Covariates				
Age			63.12 (10.76)	33–86
Female	0	171 (56.80)		
NH White	0	260 (86.40)		
Minoritized	0	41 (13.40)		
Black		24 (7.84)		
Native American/Alaska Native		4 (1.31)		
Hispanic		9 (2.94)		
Others		4 (1.31)		
MIDUS 2	0	181 (60.1)		
Socioeconomic Status				
Highest educational attainment (bachelor's degree or above)	0	164 (54.50)		
Health Locus of Control (HLOC)				
Internal HLOC	0		6.18 (0.69)	2.5–7
External HLOC	0		3.05 (1.28)	1–7
Cancer-Related Variables	94			
Cancer type				
Breast		37 (12.29)		
Cervical		17 (5.65)		
Colon		8 (2.66)		
Lung		4 (1.33)		
Lymphoma/leukemia		5 (1.66)		
Ovarian		3 (1.00)		
Prostate		21 (6.98)		
Skin		70 (23.3)		
Uterine		11 (3.65)		
Others		45 (14.95)		
Reported multiple cancer		11 (3.65)		
Years of survivorship	96		14.58 (10.59)	2–55
Long-term survivors (≥5 years)	96	170 (82.9)		
Health-Related Variables				
Ever smoked	0	144 (47.80)		
Mean BMI (kg/m^2)	0		29.51 (6.15)	17.95–63.19
< 25 kg/m^2		74 (24.60)		
25- < 30 kg/m^2		96 (31.90)		
≥30 kg/m^2		131 (43.50)		
Taking medication and/or had treatment	0	270 (89.70)		
Taking prescription medication	0	267 (88.70)		
Ever had chemotherapy	59	32 (10.60)		
Ever had immunosuppressive therapy	59	4 (1.30)		
Number of symptoms and chronic conditions	0		5.89 (3.14)	1–23
Inflammation				
Prior to transformation (winsorized)				
IL-6 (pg/mL)	0		3.16 (2.27)	0.34–10.00
CRP (mg/L)	0		2.59 (2.67)	0.15–10.00
Ln transformed				
IL-6 (*ln*; pg/mL)	0		0.91 (0.71)	−1.07–2.30
CRP (*ln*; mg/L)	0		0.45 (1.03)	−1.89–2.30

those reported cancer types, 11 mentioned multiple types of cancer diagnosis. The mean years of cancer survivorship (based on age during the MIDUS Biomarker protocol minus the reported age when cancer was diagnosed) was 14.58 years (ranges = 2–55 years).

Measures

Educational attainment

Socioeconomic status (SES) was measured using participants' highest level of formal education (0 = no bachelor's degree, 1 = bachelor's degree or higher).

Health locus of control

The measure for health locus of control (HLOC) in the MIDUS study was adapted from the Whitehall Health Survey (Marmot et al., 1991) that includes internal and external HLOC. Internal health locus was measured using four items on a 7-point Likert scale (1 = strongly agree to 7 = strongly disagree), and participants were asked to indicate that they agreed or disagreed with the following statements (four items, $\alpha = .71$): 1) Keeping healthy depends on things that I can do; 2) there are certain things I can do for myself to reduce the risk of a heart attack; 3) there are certain things I can do for myself to reduce the risk of getting cancer; 4) I work hard at trying to stay healthy. External health locus of control was measured using two items indicating how much one feels others impact their health using the same 7-point Likert scale. Participants responded to the following statements (two items, $\alpha = .30$): 1) When I am sick, getting better is in the doctor's hands; and 2) It is difficult for me to get good medical care. Items were reverse-coded, and mean scores were calculated for internal and external HLOC. Internal and external HLOC were computed for cases with valid values for at least one item. A higher score indicates a stronger sense of internal or external HLOC. This HLOC measure has been used in previous studies on health disparities (Bobak et al., 2000, Grzywacz & Marks, 2000; Lachman & Weaver, 1998), including analyses that utilized biological indicators of chronic diseases as outcomes (Fitzgerald & Papp, 2024; Zilioli et al., 2015). The bivariate correlation between internal and external HLOCs was low ($r = 0.01$, $p > 0.5$), indicating low overlap between the two scales.

Inflammatory activity

We included two inflammatory biomarkers, interleukin-6 (IL-6) and C-reactive protein (CRP). Serum IL-6 was analyzed using enzyme-linked immunosorbent assay (R&D ELISA, Minneapolis, MN) by the BioCore Lab at the University of Wisconsin. The assay range was 1.58–488 pg/mL, intra-assay coefficient of variabilities (CVs) were 3.25% (in MIDUS 2) and 4.73% (in MIDUS R), and the inter-assay CVs were 5–15% (in both MIDUS 2 and MIDUS R). Serum CRP was measured using a particle-enhanced immunonephelometric assay (BNII nephelometer, Dade Behring Inc., Deerfield, IL) at the Laboratory of Clinical Biochemistry (University of Vermont). The assay range was 0.014–216 ug/mL, intra-assay CVs were 2.2–4.1% (both in MIDUS 2 and MIDUS R), and inter-assay CVs were 4.72–5.16% (both in MIDUS 2 and MIDUS R). Following the recommendation from MacGiollabhui et al. (2020), IL-6 and CRP values were winsorized

at 10 (pg/mL for IL-6 and mg/L for CRP) to handle outliers. Log-transformed values were used for both IL-6 and CRP to normalize the distribution and reduce skewness.

Covariates

Analyses were adjusted for age (years), sex (0 = female, 1 = male), cohort (0 = MIDUS R, 1 = MIDUS 2), race/ethnicity (0 = nonwhite, 1 = white), BMI (weight kg/height m^2), and smoking status (0 = never smoked, 1 = have smoked), taking Rx and ever had chemotherapy or immunosuppressive therapy (0 = No, 1 = Yes), and number of symptoms and chronic conditions. The number of symptoms and chronic conditions was based on the report of 22 chronic conditions and symptoms (e.g. high blood pressure, diabetes, asthma, depression, and alcoholism).

Statistical analysis

Our analyses were divided into two parts. Prior to testing the mediational hypotheses, we examined whether educational attainment and (internal and external) HLOC were associated with the two inflammatory proteins using regression analysis. The second part of the analysis examined the mediational role of internal and external HLOC on the association between educational attainment and markers of inflammation. All analyses were conducted in R, and a significant association was based on an alpha lower than .05.

Regression analysis

Regression analyses were conducted to determine if there were associations among educational attainment, internal and external HLOC, and markers of inflammation. The association between predictors (i.e. educational attainment and HLOC) and CRP and IL-6 was tested in separate models. For each marker of inflammation, first, we added educational attainment as the main predictor in the model, adjusted for age, sex, and cohort (MODEL 1). HLOC and race/ethnicity were then added to the model as additional predictors (MODEL 2). In the fully adjusted regression models, BMI, smoking status, taking Rx and ever had chemotherapy or immunosuppressive therapy, and number of symptoms and chronic conditions were added as additional covariates. Regression analyses were conducted using *lm* function in R.

Mediation analysis

Formal mediation analyses were conducted to determine if internal and external HLOC measures mediated the relationship between educational attainment and inflammation. Mediation analyses for CRP and IL6 were conducted separately. Mediation analyses were conducted with the PROCESS package in R and used 10 000 bootstrapped samples (Hayes & Rockwood, 2017). Mediation analyses were adjusted for all covariates.

Missing data

Missing data were minimal in the dataset and handled using listwise deletion during the regression analyses.

Results

Descriptive statistics

Table 1 displays the descriptive statistics for participants' demographic characteristics, educational attainment, internal and external health locus of control, markers of inflammation, and other health-related variables. The average age of participants during the survey was 63.12 years ($SD = 10.76$). Among the participants, 56.80% were female, 86.40% were non-Hispanic (NH) white, and 54.50% have a bachelor's degree or higher. The mean internal HLOC score was 6.18 ($SD = 0.69$), and the mean external HLOC score was 3.05 ($SD = 1.28$). After natural log adjustments, the mean level of IL-6 was 0.91 ($SD = 0.71$) and CRP was 0.45 ($SD = 1.03$).

Results from regression analyses

Educational attainment, internal HLOC, and IL-6

The results from regression analysis among educational attainment, internal HLOC, and IL-6 are presented in Table 2. Adjusted for age, sex, and cohort (MODEL 1), having a bachelor's degree or higher was associated with lower IL-6 ($b = -0.16$, $SE = 0.08$, 95% $CI = [-0.32, -0.01]$). However, the association between educational attainment and IL-6 became non-significant after adjusting for race/ethnicity and internal HLOC (MODEL 2) ($b = -0.11$, $SE = 0.08$, 95% $CI = [-0.64, 0.04]$). Internal HLOC was significantly inversely associated with IL-6 ($b = -0.18$, $SE = 0.06$, 95% $CI = [-0.29, -0.08]$), suggesting that lower internal HLOC was associated with elevated IL-6. After adding BMI and smoking status to the model (MODEL 3), the association between educational attainment and IL-6 remained non-significant ($b = -0.10$, $SE = 0.07$, 95% $CI = [-0.24, 0.05]$). In contrast, the association between internal HLOC and IL-6 remained significant, while the magnitude was slightly attenuated ($b = -0.12$, $SE = 0.05$, 95% $CI = [-0.22, -0.02]$).

Educational attainment, internal HLOC and CRP

The results from the multiple regression analysis among educational attainment, internal HLOC and CRP are shown in Table 2. In the model adjusted for age, sex, and cohort (MODEL 1), there was a significant association between educational attainment and CRP ($b = -0.37$, $SE = 0.12$, 95% $CI = [-0.60, -0.14]$). In the model adjusting for age, sex, cohort, and race/ethnicity (MODEL 2), the significant negative association between educational attainment and CRP remained despite slightly attenuated in magnitude ($b = -0.32$, $SE = 0.12$, 95% $CI = [-0.55, -0.09]$). Similarly, we observed significant negative association between internal HLOC and CRP ($b = -0.23$, $SE = 0,08$, 95% $CI = [-0.39, -0.07]$). In the fully adjusted model (MODEL 3), lower educational attainment remained significantly associated with elevated CRP ($b = -.28$, $SE = 0.11$, 95% $CI = [-0.50, -0.06]$). However, the association between internal HLOC and CRP became non-significant in the fully adjusted model ($b = -0.14$, $SE = 0.08$, 95% $CI = [-0.29, -0.02]$).

Educational attainment, external HLOC and IL-6

The results of the regression analysis among educational attainment, external HLOC, and IL-6 are shown in Table 3. Similar to the results involving internal HLOC, the significant association between educational attainment and IL-6 became non-significant after

Table 2. Results from regression analysis involving educational attainment, internal HLOC, and markers of inflammation.

	MODEL 1			MODEL 2			MODEL 3		
Predictor	*b* (*SE*)	beta	95%CI	*b* (*SE*)	beta	95%CI	*b* (*SE*)	beta	95%CI
Internal HLOC and IL6									
Intercept	−0.23 (0.24)	–	[−0.70, 0.24]	**1.08 (0.40)**	–	**[0.29, 1.87]**	−0.59 (0.44)	–	[−1.46, 0.28]
Educational attainment (0 = no bachelor's degree, 1 = bachelor's degree or higher)	**-0.16 (0.08)**	**−0.11**	**[−0.32, −0.01]**	−0.11 (0.08)	−0.11	[−0.64, 0.04]	−0.10 (0.07)	−0.07	[−0.24, 0.05]
Internal HLOC (score)	–	–	–	**-0.18 (0.06)**	**−0.18**	**[−0.29, −0.08]**	**-0.12 (0.05)**	**−0.12**	**[−0.22, −0.02]**
Age (years)	**0.02 (0.00)**	**0.30**	**[0.01, 0.03]**	**0.02 (0.00)**	**0.32**	**[0.01, 0.03]**	**0.02 (0.00)**	**0.27**	**[0.01, 0.03]**
Sex (0 = female, 1 = male)	0.07 (0.08)	0.05	[−0.09, 0.23]	0.05 (0.08)	0.03	[−0.11, 0.20]	0.05 (0.07)	0.04	[−0.09, 0.20]
Cohort (0 = MR, 1 = M2)	−0.07 (0.08)	−0.05	[−0.23, 0.09]	−0.05 (0.08)	−0.04	[−0.21, 0.10]	−0.01 (0.07)	−0.01	[−0.15, 0.13]
Race/ethnicity (0 = minoritized, 1 = NH white)				**-0.35 (0.11)**	**−0.17**	**[−0.57, −0.13]**	**-0.26 (0.10)**	**−0.13**	**[−0.46, −0.06]**
BMI (kg/m^2)							**0.03 (0.01)**	**0.30**	**[0.02, 0.05]**
Ever smoked (0 = No, 1 = Yes)							0.10 (0.07)	0.07	[−0.04, 0.23]
Taking Rx and ever had chemotherapy or immunosuppressive therapy (0 = No, 1 = Yes)							**0.30 (0.12)**	**0.13**	**[0.06, 0.54]**
Number of symptoms and chronic conditions							0.02 (0.01)	0.08	[−0.01, 0.04]
Model Summary		*R*-sq = .11 **F (4, 296) = 9.43**			*R*-sq = .17 **F (6, 294) = 10.12**			*R*-sq = .31 **F (10, 290) = 12.77**	
Internal HLOC and CRP									
Intercept	0.39 (0.36)	–	[−0.32, 1.09]	**1.92 (0.62)**	–	**[0.71, 3.13]**	−0.73 (0.67)	–	[−2.05, 0.60]
Educational attainment (0 = no bachelor's degree, 1 = bachelor's degree or higher)	**-0.37 (0.12)**	**-0.18**	**[−0.60, −0.14]**	**-0.32 (0.12)**	**−0.16**	**[−0.55, −0.09]**	**-0.28 (0.11)**	**−0.14**	**[−0.50, −0.06]**
Internal HLOC (score)	–	–	–	**-0.23 (0.08)**	**−0.16**	**[−0.39, −0.07]**	−0.14 (0.08)	−0.09	[−0.29, 0.02]
Age (years)	0.01 (0.01)	0.06	[−0.01, 0.02]	0.01 (0.01)	0.07	[−0.00, 0.02]	0.00 (0.01)	0.03	[−0.01, 0.01]
Sex (0 = female, 1 = male)	**-0.29 (0.12)**	**−0.14**	**[−0.53, −0.05]**	**-0.33 (0.12)**	**−0.16**	**[−0.56, −0.09]**	**-0.32 (0.11)**	**−0.16**	**[−0.55, −0.10]**
Cohort (0 = MR, 1 = M2)	0.08 (0.12)	0.04	[−0.15, 0.32]	0.10 (0.12)	0.05	[−0.13, 0.34]	0.17 (0.11)	0.08	[−0.05, 0.38]
Race/ethnicity (0 = minoritized, 1 = NH white)				−0.28 (0.17)	−0.09	[−0.61, 0.06]	−0.15 (0.16)	−0.05	[−0.45, 0.16]
BMI (kg/m^2)							**0.06 (0.01)**	**0.35**	**[0.04, 0.08]**
Ever smoked (0 = No, 1 = Yes)							0.12 (0.11)	0.06	[−0.09, 0.34]
Taking Rx and ever had chemotherapy or immunosuppressive therapy (0 = No, 1 = Yes)							0.31 (0.19)	0.09	[−0.06, 0.67]
Number of symptoms and chronic conditions							0.02 (0.02)	0.06	[−002, 0.06]
Model Summary		*R*-sq = .06 **F (4, 296) = 4.78**			*R*-sq = .09 **F (6, 294) = 4.92**			*R*-sq = .24 **F (10, 290) = 9.26**	

Note: b = unstandardized regression coefficient, beta = standardized regression coefficient, SE = standard error, CI = confidence interval, R-sq = *R*-squared. Bolded number indicate significant association at *p*-value < .05.

Table 3. Results from regression analysis involving educational attainment, external HLOC, and markers of inflammation.

	MODEL 1			MODEL 2			MODEL 3		
Predictor	*b* (*SE*)	beta	95% *CI*	*b* (*SE*)	beta	95% *CI*	*b* (*SE*)	beta	95% *CI*
External HLOC and IL6									
Intercept	−0.23 (0.24)	–	[−0.70, 0.24]	−0.21 (0.27)	–	[−0.74, 0.32]	**-1.47 (0.31)**	–	**[−2.07, −087]**
Educational attainment (0 = no bachelor's degree, 1 = bachelor's degree or higher)	**-0.16 (0.08)**	**−0.11**	**[−0.32, −0.01]**	−0.10 (0.08)	−0.07	[−0.25, 0.06]	−0.09 (0.07)	−0.06	[−0.24, 0.06]
Internal HLOC (score)	–	–	–	**0.07 (0.03)**	**0.12**	**[0.01, 0.13]**	0.04 (0.03)	0.07	[−0.02, 0.09]
Age (years)	**0.02 (0.00)**	**0.30**	**[0.01, 0.03]**	**0.02 (0.00)**	**0.31**	**[0.01, 0.03]**	**0.02 (0.00)**	**0.25**	**[0.01, 0.02]**
Sex (0 = female, 1 = male)	0.07 (0.08)	0.05	[−0.09, 0.23]	0.09 (0.08)	0.06	[−0.07, 0.25]	0.08 (0.07)	0.06	[−0.06, 0.23]
Cohort (0 = MR, 1 = M2)	−0.07 (0.08)	−0.05	[−0.23, 0.09]	−0.08 (0.08)	−0.05	[−0.23, 0.08]	−0.02 (0.07)	−0.02	[−0.17, 0.12]
Race/ethnicity (0 = minoritized, 1 = NH white)				**-0.32 (0.11)**	**−0.16**	**[−0.54, −0.10]**	**-0.24 (0.10)**	**−0.12**	**[−0.45, −0.04]**
BMI (kg/m^2)							**0.04 (0.01)**	**0.31**	**[0.02, 0.05]**
Ever smoked (0 = No, 1 = Yes)							0.09 (0.07)	0.06	[−0.06, 0.23]
Taking Rx and ever had chemotherapy or immunosuppressive therapy (0 = No, 1 = Yes)							**0.31 (0.12)**	**0.13**	**[0.07, 0.55]**
Number of symptoms and chronic conditions							0.02 (0.02)	0.08	[−0.01, 0.04]
Model Summary		*R*-sq = .11 **F (4, 296) = 9.43**			*R*-sq = .15 **F (6, 294) = 8.86**			*R*-sq = .30 **F (10, 290) = 12.20**	
External HLOC and CRP									
Intercept	0.39 (0.36)	–	[−0.32, 1.09]	0.12 (0.40)	–	[−0.67, 0.91]	−1.85 (0.46)	–	[−2.76, 0.94]
Educational attainment (0 = no bachelor's degree, 1 = bachelor's degree or higher)	**-0.37 (0.12)**	**−0.18**	**[−0.60, −0.14]**	**-0.28 (0.12)**	**−0.13**	**[−0.51, −0.04]**	**-0.25 (0.11)**	**−0.12**	**[−0.47, −0.03]**
Internal HLOC (score)	–	–	–	**0.14 (0.05)**	**0.17**	**[0.05, 0.23]**	**0.10 (0.04)**	**0.12**	**[0.01, 0.18]**
Age (years)	0.01 (0.01)	0.06	[−0.01, 0.02]	0.01 (0.01)	0.06	[−0.01, 0.02]	0.00 (0.01)	0.02	[−0.01, 0.01]
Sex (0 = female, 1 = male)	**-0.29 (0.12)**	**−0.14**	**[−0.53, −0.05]**	**-0.26 (0.12)**	**−0.13**	**[−0.50. −0.03]**	**-0.28 (0.11)**	**-0.14**	**[−0.50, −0.06]**
Cohort (0 = MR, 1 = M2)	0.08 (0.12)	0.04	[−0.15, 0.32]	0.06 (0.12)	0.03	[−0.17, 0.30]	0.14 (0.11)	0.07	[−0.08, 0.35]
Race/ethnicity (0 = minoritized, 1 = NH white)				−0.23 (0.17)	−0.08	[−0.56, 0.10]	−0.12 (0.16)	−0.04	[−0.43, 0.19]
BMI (kg/m^2)							**0.06 (0.01)**	**0.35**	**[0.04, 0.08]**

(*Continued*)

Table 3. (Continued).

	MODEL 1			MODEL 2			MODEL 3		
Predictor	*b* (*SE*)	beta	95% *CI*	*b* (*SE*)	beta	95% *CI*	*b* (*SE*)	beta	95% *CI*
Ever smoked (0 = No, 1 = Yes)							0.10 (0.11)	0.05	[−0.11, 0.31]
Taking Rx and ever had chemotherapy or immunosuppressive therapy (0 = No, 1 = Yes)							0.30 (0.18)	0.09	[−0.07, 0.66]
Number of symptoms and chronic conditions							0.02 (0.02)	0.06	[−0.02, 0.06]
Model Summary		*R*-sq = .06 **F (4, 296) = 4.78**			*R*-sq = .10 **F (6, 294) = 5.16**			*R*-sq = .25 **F (10, 290) = 9.53**	

Note: b = unstandardized regression coefficient, beta = standardized regression coefficient, SE = standard error, CI = confidence interval, R-sq = *R*-squared. Bolded number indicate significant association at *p*-value < .05.

external HLOC and race/ethnicity added in the model ($b = -.10$, $SE = 0.08$, 95% $CI = [-0.25, 0.06]$). On the other hand, higher external HLOC was significantly associated with elevated IL-6 ($b = 0.07$, $SE = 0.03$, 95% $CI = -[0.01, 0.13]$). However, the association between external HLOC and IL-6 became non-significant in the fully adjusted model ($b = 0.04$, $SE = 0.03$, 95% $CI = [-0.02, 0.09]$).

Educational attainment, external HLOC and CRP

Table 3 includes results from regression analysis among educational attainment, external HLOC, and CRP. Educational attainment was consistently associated with CRP, even after adjusting for external HLOC, race/ethnicity, and health-related covariates (MODEL 2: $b = -0.28$, $SE = 0.12$, 95% $CI = [-0.51, -0.04]$; MODEL 3: $b = -0.25$, $SE = 0.11$, 95% $CI = [-0.47, -0.03]$). External HLOC was significantly associated with CRP in the minimally adjusted model (MODEL 2: $b = 0.14$, $SE = 0.05$, 95% $CI = [0.05, 0.23]$), showing that greater external HLOC was associated with elevated CRP. In the fully adjusted model, external HLOC remained significantly associated with CRP despite slight attenuation in the magnitude of the association ($b = 0.10$, $SE = 0.04$, 95% $CI = [0.01, 0.18]$).

Results from mediation analysis

Based on the preliminary analyses above, educational attainment and HLOC were associated with CRP, but not IL-6. Thus, we only conducted the mediation analysis involving educational attainment, HLOC, and CRP. The results from the mediation analysis are presented in Table 4 and Figure 1. Lower educational attainment was associated with greater external HLOC ($a_2 = -0.50$, $SE = 0.15$, 95% $CI = [-0.80, -0.21]$), but not internal HLOC ($a_1 = 0.11$, $SE = 0.08$, 95% $CI = [-0.06, 0.27]$). In turn, greater external HLOC was associated with elevated CRP ($b_2 = 0.10$, $SE = 0.04$, 95% $CI = [0.01, 0.18]$). Internal HLOC was not associated with CRP ($b_1 = -0.14$, $SE = 0.08$, 95% $CI = [-0.29, 0.01]$). The direct path between educational attainment and CRP remained significant (direct effect/$c' = -0.23$, $SE = 0.11$, 95% $CI = [-0.45, -0.01]$; total effect/$c = -0.29$, SE = 0.11, 95% $CI = [-0.51, -0.08]$). The indirect effect through external HLOC on the association between educational attainment and CRP was significant (effect = −0.05, bootstrapped $SE = 0.02$, 95% CI [bootstrapped] = [−0.10, −0.01]). In summary, higher external HLOC was a significant path through which lower educational attainment was associated with elevated CRP.

Discussion

Using a national study of middle-aged and older adults' cancer survivors in the U.S., this study examined the association between educational attainment, internal and external health locus of control (HLOC), and inflammation in this population. We found that among adult cancer survivors, HLOC was an important psychosocial pathway in the association between lower educational attainment and elevated inflammatory activity, a robust biological predictor for age-related chronic diseases. Specifically, we found that cancer survivors with lower educational backgrounds may perceive that their health is highly influenced by external control, which in turn is associated with elevated inflammation, especially CRP.

Table 4. Results from mediation analysis involving education, HLOC, and CRP.

	Education→Internal and External HLOC→CRP								
	(M1) Internal HLOC			(M2) External HLOC			(Y) CRP (*ln*)		
Predictor	*b* (*SE*)	beta	95% *CI*	*b* (*SE*)	beta	95% *CI*	*b* (*SE*)	beta	95% *CI*
Intercept	**6.40 (0.34)**	–	**[5.73, 7.07]**	**2.53 (0.62)**	–	**[1.32, 3.74]**	−0.96 (0.67)	–	[−2.29, 0.37]
(X) Educational attainment (0 = no bachelor's degree, 1 = bachelor's degree or higher)	0.11 (0.08)	0.16	[−0.06, 0.27]	**-0.50 (0.15)**	**−0.39**	**[−0.80, −0.21]**	**-0.23 (0.11)**	**−0.22**	**[−0.45, −0.01]**
(M1) Internal HLOC (score)	–	–	–	–	–	–	−0.14 (0.08)	−0.09	[−0.29, 0.01]
(M2) External HLOC (score)	–	–	–	–	–	–	**0.10 (0.04)**	**0.12**	**[0.01, 0.18]**
Age (years)	0.01 (0.00)	0.11	[−0.00, 0.02]	−0.00 (0.01)	−0.01	[−0.02, 0.01]	0.00 (0.01)	0.03	[−0.01, 0.01]
Sex (0 = female, 1 = male)	**-0.19 (0.08)**	**−0.13**	**[−0.35, −0.02]**	−0.17 (0.15)	−0.06	[−0.47, 0.13]	**-0.31 (0.11)**	**−0.15**	**[−0.53, −0.09]**
Cohort (0 = MR, 1 = M2)	0.04 (0.08)	0.03	[−0.12, 0.20]	0.22 (0.15)	0.08	[−0.08, 0.51]	0.14 (0.11)	0.07	[−0.07, 0.36]
Race/ethnicity (0 = minoritized, 1 = NH white)	−0.09 (0.12)	−0.05	[−0.32, 0.14]	−0.15 (0.21)	−0.04	[−0.57, 0.27]	−0.13 (0.16)	−0.04	[−0.44, 0.18]
BMI (kg/m^2)	**-0.01 (0.01)**	**−0.13**	**[−0.03, −0.00]**	0.01 (0.01)	0.07	[−0.01, 0.04]	**0.06 (0.01)**	**0.34**	**[0.04, 0.07]**
Ever smoked (0 = No, 1 = Yes)	0.02 (0.08)	0.02	[−0.13, 0.18]	0.20 (0.15)	0.08	[−0.09, 0.48]	0.11 (0.11)	0.05	[−0.11, 0.32]
Taking Rx and ever had chemotherapy or immunosuppressive therapy (0 = No, 1 = Yes)	−0.16 (0.14)	−0.07	[−0.43, 0.11]	0.37 (0.25)	0.09	[−0.13, 0.86]	0.27 (0.18)	0.08	[−0.09, 0.63]
Number of symptoms and chronic conditions	−0.01 (0.01)	−0.03	[−0.03, 0.02]	0.01 (0.03)	0.02	[−0.04, 0.06]	0.02 (0.02)	0.06	[−0.02, 0.06]
Model Summary	*R*-sq = .05			*R*-sq = .08			*R*-sq = .26		
	F (9, 291) = 2.98			**F (9, 291) = 2.98**			**F (11, 289) = 9.03**		
Total Effect				*b* (*SE*)		Beta	95% *CI*		
Education→CRP				**-0.29 (0.11)**		**−0.29**	**[−0.51, −0.08]**		
Indirect Effects				*Effect (boot. SE)*			95% *CI (boot.)*		
Education→Internal HLOC→CRP				−0.02 (0.01)			[−0.05, 0.01]		
Education→External HLOC→CRP				**-0.05 (0.02)**			**[−0.10, −0.01]**		
Total Indirect Effects				**-0.06 (0.03)**			**[−0.12, −0.01]**		
Partially Standardized Indirect Effects									
Education→Internal HLOC→CRP				−0.02 (0.01)			[−0.05, 0.01]		
Education→External HLOC→CRP				**-0.05 (0.02)**			**[−0.10, −0.01]**		
Total Indirect Effects				**-0.06 (0.03)**			**[−0.12, −0.01]**		

Note: *b* = unstandardized regression coefficient, beta = standardized regression coefficient, *SE* = standard error, *CI* = confidence interval, R-sq = *R*-squared., boot. *SE* = bootstrapped standard error, and *CI* (boot.) = bootstrapped confidence interval. Bolded numbers indicate significant association at *p*-value < .05. X = independent variable, M1 = mediator 1 (internal HLOC), M2 = mediator 2 (external HLOC), and Y = dependent variable.

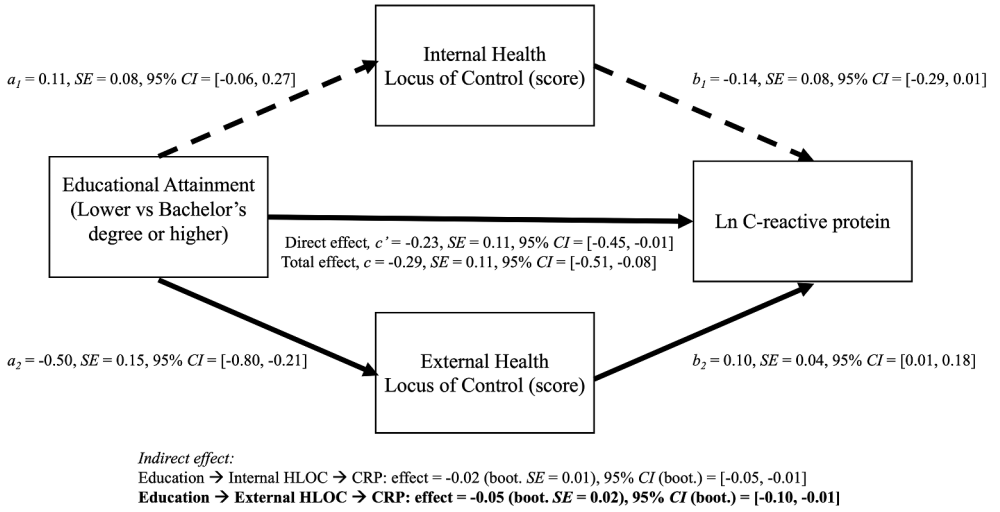

Figure 1. Summary of findings from mediation analysis involving educational attainment, external health locus of control, and c-reactive protein (CRP; *ln*). The findings indicate significant pathways through higher external HLOC, but not internal HLOC, on the association between lower education and elevated CRP.

First, we hypothesized that lower educational attainment would be associated with inflammation among cancer survivors. Our results confirmed an association between lower SES and elevated CRP but not IL-6 among cancer survivors in our sample. One reason for this difference may be that CRP levels offer a long-term reflection of hepatic function and general health whereas IL-6 reflects acute responses to inflammatory stimuli as well as the extent of a person's adiposity. The increased release of IL-6 also precedes a rise in CRP levels because IL-6 is one of the potent stimulators of CRP synthesis and secretion (Del Giudice & Gangestad, 2018). These differences may also be observed because our sample comprises cancer survivors. Studies suggest that levels of CRP provide a more sensitive indication of prognosis among cancer survivors, while IL-6 is a more salient bioindicator of a cancer diagnosis (Groblewska et al., 2008; Ravishankaran & Karunanithi, 2011). The significant association between lower SES and CRP among cancer survivors may indicate the higher exposure to chronic stressors due to cancer diagnosis, treatment, and maintenance (Lantz et al., 2005), which can contribute to accelerated aging (Yegorov et al., 2020).

Second, we hypothesized that lower internal HLOC and higher external HLOC were associated with elevated inflammation. We found that greater internal HLOC was consistently associated with lower inflammation, using both measures of CRP and IL-6. This is consistent with literature showing that a greater sense of control is associated with elevated inflammation (Magin et al., 2024; Zahodne et al., 2019). One reason may be that positive psychosocial beliefs can reduce stress and motivate people to engage in health-promoting behavior (Lachman & Schiloski, 2024). Furthermore, our results show that greater external HLOC was only significantly associated with elevated CRP, but not IL-6. As stated previously, CRP is more of a downstream measure of inflammation, reflecting racial and socioeconomic disparities more than other measures (Farmer et al.,

2021). It is also hypothesized that structural and environmental disadvantages influence external measures of perceived control, whereas internal factors are shaped by an individual's microenvironment, including family or peers (Zahodne, 2021). Therefore, external HLOC and CRP are each more closely linked to differences in educational background.

Finally, we hypothesized that lower internal HLOC and higher external HLOC were significant pathways through which lower educational attainment was associated with elevated inflammation. We found robust evidence that external HLOC was an important psychosocial pathway in the association between lower educational attainment and elevated CRP. This finding was consistent with the framework developed by Matthews and colleagues on the important role of psychosocial factors in explaining socioeconomic disparities in health and aging (Matthews et al., 2010). Others have documented the mediating role of general perceived control on the association between SES and aging phenotype, such as frailty (Mooney et al., 2018). We contributed to this body of work by showing that differences in educational attainment among cancer survivors are associated with differences in psychosocial resources, which can lead to disparities in biological markers of aging. We showed that formal education is an important social context in the formation of locus of control, including health locus of control. We corroborated previous studies that showed an association between lower educational attainment and greater external locus of control (Grotz et al., 2011; Mitchell et al., 2018). Furthermore, greater external HLOC among cancer survivors may be an individual reflection of social and structural inequality that can lead to a lack of belief in control over health and other life outcomes (Mirowsky & Ross, 2007). This can lead to a lack of motivation in adhering to treatment, medication, and health-promoting behaviors. Thus, we observed greater external HLOC as a significant pathway in the association between lower educational attainment and elevated CRP.

Contrary to our hypothesis, we did not find evidence of the significant role of internal HLOC on the pathway between educational attainment and CRP. Internal HLOC may play important role among cancer survivors who are diagnosed at earlier stages (stage I and II) (Rehman, 2022). Unfortunately, the MIDUS study did not collect information regarding the staging of cancer diagnosis. Future studies should prioritize analyzing the role of HLOC based on cancer staging, as an important psychosocial pathway linking educational attainment and biological indicators of morbidity and mortality. The majority of participants in our study are long-term cancer survivors. Our findings on the relative important role of external HLOC compared to internal HLOC may be relevant to long-term cancer survivorship. However, replications are needed with a larger and more diverse sample.

Given the significant proportion of aging cancer survivors in the United States (Tonorezos et al., 2024), it is imperative to better understand the biological, psychological, and social factors contributing to maintaining health and well-being and achieving healthy aging in this population (Ness & Wogksch, 2020; Sedrak et al., 2021). While social and structural changes, especially related to universal healthcare reform, would be of high priority to achieve equity in healthy aging among cancer survivors, identifying possible feasible individual-level intervention avenues is still essential. Identifying important psychosocial factors of health that link to socioeconomic and racial disparities in healthy aging among cancer survivors is a promising area for research and translational

efforts. In this study, we contribute to this effort by clarifying the roles of HLOC in the link between educational attainment and an important biological marker of aging. Addressing the higher levels of external HLOC – feeling of having no control over one's health outcomes – among lower SES cancer survivors may be an important intervention opportunity. While this could be challenging, given that external HLOC could be a reflection of structural barriers in accessing healthcare, finding ways to empower cancer survivors' sense of control in their health is a promising avenue of research.

Limitations

The selection of cancer survivors from the pool of the MIDUS study participants was based on self-report, which is prone to bias. However, MIDUS participants also reported their cancer history during the baseline survey, so we were able to clarify the report of cancer diagnosis based on two separate sources for each participant. Furthermore, although the MIDUS study was not specifically designed to investigate cancer survivorship, the age of the participants (i.e. middle-aged and older adults) allowed us to pool a significant number of cancer survivors. The MIDUS study provided a unique opportunity to link social, psychosocial, and biological health and aging factors. Another limitation was the lack of racial and socioeconomic diversity (majority NH white and had attained a bachelor's degree) in the MIDUS sample. Utilizing samples that are more diverse socioeconomically and racially, future studies should assess the intersectional role between socioeconomic factors and race/ethnicity more comprehensively on the associations between HLOC and inflammation, given the clear evidence of racial disparities in survivorship outcomes in the United States (for example, Lee et al., 2024). Given that racial discrimination combined with low SES likely plays a role in an individual's perception of external HLOC, it is critical to study this topic among socioeconomically and racially diverse cancer survivors.

In addition, the data used in this analysis were cross-sectional, meaning that causation cannot be inferred. Although mediation analyses inherently assess causal pathways, we were limited in inferring causation given the nature of data used in this study. So, the results of the mediation analysis must be taken cautiously. Furthermore, we did not apply corrections for multiple comparisons for a more robust conclusion. Our goal was to clarify the pathways among educational attainment, internal and external HLOC, and inflammation, and we found promising preliminary findings based on the results of this analysis. Future studies should prioritize utilizing longitudinal data and take advantage of the temporal aspect among these factors to replicate if HLCO, especially external HLOC, indeed mediated the link between lower SES and elevated risk of age-related chronic diseases. Lastly, future studies should assess how these pathways persist among patients of different types of cancer. While our study included cancer survivors of several types of cancer, our analysis did not consider differences in HLOC among these experiences. It would be meaningful to understand how these relationships differ among patients with different types of cancer.

Conclusion

This work is among the first to investigate the mediational role of health locus of control in the relationship between educational attainment and inflammation, an important biological marker of healthy aging, among cancer survivors. We found that cancer survivors from lower educational backgrounds may perceive their health as outside of their control, demonstrated by lower measures of external HLOC. Lower educational attainment and lack of control in health outcomes may not only lead to elevated inflammation but may compound treatment-related inflammation resulting in a higher risk for age-related chronic diseases and compromised healthy aging.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Data from the MIDUS study is publicly available on the MIDUS Colectica Portal (https://midus.colectica.org/). The analyses in this study were not preregistered.

Ethics statement

The MIDUS protocol was approved by the Health Sciences Institutional Review Board at the University of Wisconsin (Madison, WI), as well as by the IRBs at Georgetown University (Washington D.C.) and UCLA (Los Angeles, CA).

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