The Implications of Response Patterns in Questions of Early Life Adverse Events on Health Status and Cognitive Function Later in Life in the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

BACKGROUND: Research suggests that early life adversity (ELA) is associated with late life cognition; however, such studies may be influenced by response bias.

OBJECTIVES: To evaluate response patterns for ELA questions by various sociodemographic characteristics and to examine whether ELA responsiveness was associated with cognitive performance and/or decline.

DESIGN: Cross-sectional study.

SETTING: The Multi-Ethnic Study of Atherosclerosis (MESA), a population-based study of subclinical atherosclerosis.

PARTICIPANTS: 3,837 participants, averaging 59 (standard deviation [SD]=9.0) years of age, with 55% women and participants from diverse backgrounds (26% Black, 13% Chinese, 21% Hispanic/Latino, 40% White: 32% non-native, and 10% Spanish speakers).

MEASUREMENTS: ELA responses assessed via a telephone survey (2018-2019) were used to examine response patterns and associated cognitive outcomes, measured using the Cognitive Abilities Screening Instrument (CASI) during MESA Exam 5 and Exam 6.

RESULTS: Spanish speakers (odds ratio [OR] 2.15, 95% confidence interval [CI]: 1.38-3.36) and participants born outside of the United States (U.S.) (OR 1.66, 95% CI: 1.18-2.33) had higher odds of ELA refusal than U.S. born ELA completers who spoke English. There were no significant differences in change in CASI score from Exam 5 to Exam 6 (beta=-0.38, [SE] 0.54, p=0.490) or Exam 6 CASI score (beta=-0.68, [SE] 0.49, p=0.168) among those who refused the ELA assessment compared to those who completed the assessment.

CONCLUSIONS: Sociodemographic factors predicted completion status on questions of ELA. There was no difference in cognitive function and change in cognition across ELA completion groups.

Keywords: Early life adversity, psychosocial, response bias, cognitive decline.

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Introduction and Context

Accumulating evidence documents the significant, long-term impact that exposure to early life adversity (ELA) has on adult health, well-being, and cognitive function (1-4). The relationship between exposure to childhood adversity and increased risk for morbidity and mortality among adults suggests that exposure to ELA may be associated with social, emotional, and cognitive deficits, which in turn have the potential to increase cumulative health risk behaviors over the lifespan (2, 5, 6). A questionnaire about adverse childhood experiences, the ACEs questionnaire, refers to sources of trauma or stress that occur before the age of 18, including emotional, physical, and sexual abuse; emotional and physical neglect, exposure to household challenges such as disorganization, domestic violence, substance abuse, mental illness, criminal behavior, and parental loss (e.g., death, separation, and divorce) (2).

Exposure to features of ELA during childhood have been reported to induce physiological changes associated with stress-related chronic health problems, which can potentially serve as precursors of disease development in later life (7). Findings from longitudinal studies investigating associations of childhood adversity over the lifespan suggest that those exposed to ELA are at elevated risk for cardiovascular disease (CVD), increased inflammation, chronic stress, obesity, and cognitive impairment in later life (1, 4-6, 8). Moreover, the American Heart Association

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(AHA) provided a scientific statement describing associations between childhood adversity and cardiometabolic health. The AHA found that childhood adversity was associated with both greater risk for cardiometabolic outcomes (obesity, hypertension, high blood pressure, diabetes, and CVD) as well as negative health behaviors (smoking, excessive alcohol consumption, and overeating) (9). Consistent with these findings, several reviews have indicated a link between childhood adversity and CVD mortality and CVD outcomes, such as myocardial infarction, stroke, ischemic heart disease, and coronary heart disease (10, 11). Further, vascular and metabolic risk factors are closely associated with cognitive decline and incidence dementia, particularly in older populations (12). The significance of these findings lie in the potential role of cardiometabolic health in connections between ELA and cognitive decline.

Response Bias

Despite evidence of subsequent health outcomes of early life adverse experiences (4-6, 8), such associations are inherently difficult to study due to challenges generated from the use of retrospective self-report data (13-15). One major concern in understanding the prevalence and long-term health impacts of exposure to ELA emanates from the elicitation of information long after the events occurred (16). Not only is there a challenge of recalling events after an extensive lapse of time (i.e., recall bias), but recalling potentially traumatic events in response to interviewer queries can potentially result in an incomplete description of events (17-19). Survey nonresponse results in the misrepresentation of a true population and can be influenced by the sociodemographic characteristics of non-responders. Particularly in questions that touch upon sensitive topics like childhood adversity, it's essential to acknowledge that certain social groups may exhibit heightened apprehension toward participating in research, often influenced by levels of trust or mistrust in the research process (17, 18). Similar underlying factors may influence those who partially vs fully respond to questionnaires, with research showing that complete respondents were more likely to be White, Non-Hispanic, and over 65 years of age (20). Given all of these challenges, it is important to better understand potential differences in response patterns and the implication for interpretation when analyzing cognitive and ELA data.

The Multi-Ethnic Study of Atherosclerosis (MESA) recently collected data on exposure to ELA, allowing us to investigate response patterns in a diverse cohort and evaluate the potential relationship between ELA and cognitive function in later life. The objective of this study was to (1) evaluate response patterns, as well as predictors of differences in response patterns for ELA questions by various sociodemographic characteristics and (2) to examine whether ELA responsiveness was associated with cognitive performance and/or decline.

Materials and methods

The MESA Cohort

MESA is a multi-site, longitudinal study that began in 2000 to investigate the prevalence, correlates, and progression of subclinical and clinical CVD (21). The baseline cohort of MESA was comprised of 6,814 adults aged 45 to 84 who self-identified as Non-Hispanic White, Non-Hispanic Black, Chinese, or Hispanic/Latino and were free from clinical CVD. Participants were recruited to MESA from six study sites across the United States: Baltimore City and County, MD; Chicago IL; Forsyth County, NC; Los Angeles County, CA; New York City, NY; and St. Paul, MN. MESA collected data from participants during 6 in-person visits and up to 22 annual telephone follow-up calls.

Early Life Adversity

Exposure to ELA was examined via a seven-item telephone assessment, adapted from the original ACEs questionnaire (2), during the 20th annual follow-up call (August 2018-August 2019). Items captured by the ELA assessment cover the following domains: parental support/affect; emotional abuse; parental physical affection; physical abuse; household substance abuse; household organization; and parental monitoring (Supplemental Table 1). Responses were measured on a Likert scale ranging from 1-6, indicating how often a participant was exposed to a particular event or experience before the age of 18: (1) never, (2) almost never, (3) sometimes, (4) fairly often, (5) very often, (6) no response. Participants who scored a 6, indicating "no response", for all 7 questions were included in the "ELA Refused" category.

Response Pattern

Response status was determined according to participants' response patterns on the assessments, categorized by the following classifications: (1) contacted but refused to respond to any ELA questions (i.e., responded "no response") or had a blank score ("Refused ELA"); (2) contacted and received the ELA assessment but only partially completed it ("ELA Partially Completed"); and (3) contacted and answered all assessment questions ("All ELA Completed"). Participants who were contacted but did not participate in the follow-up 20 exam were not included in our analyses because of noninformative missingness.

Assessment of Cognition

Global cognitive function was evaluated at MESA Exam 5 (2010-2012) and 6 (2016-2018) using the Cognitive Abilities Screening Instrument (CASI, version 2) (22). The CASI is a 25-item test of global cognitive function (scale 0-100) (22). Higher CASI scores indicated better global cognitive function. Arithmetic change in CASI score from Exam 5 to Exam 6 was used to measure cognitive decline. Participants with a missing or invalid CASI score (defined as scores below 20 or those missing more than three questions) were excluded from these analyses.

Covariates

Participant demographics included age, gender, race and ethnicity, level of education, income, and depressive symptoms, all self-reported at baseline (2000-2002). Measures of wealth and parental education obtained at Exam 2 (2002-2004) were also assessed. Potential confounders were considered based on prior studies documenting the association of ELA exposure with the (23). Socioeconomic status (SES) was captured using indicators of both adult and childhood SES. Adult SES was reflected by participants' income and highest level of education reported at Exam 1. For our analyses, income was collapsed into two separate categories: <$75,000 and >=$75,000. We categorized education by those with a high school degree or greater and those with less than a high school degree. We also considered measures of wealth to reflect adult SES, which were collected at Exam 2. Wealth variables included: (1) whether the participant, or their family, had investments including stocks, bonds, mutual funds, retirement investments, or other investments (yes/no), (2) whether the participant owned their home (rent/mortgage/own/other), (3) whether the participant owned a car (yes, 1 car/no/yes, >1 car), and (4) whether the participant owned land or property that was not their primary residence (yes/no/currently buying). The highest level of education attained by a participants' mother or father at Exam 2 was used to indicate childhood SES.

As cultural factors may influence how a person responds to sensitive questions, we selected proxy measures of acculturation, including indicators of participants' language spoken at Exam 1, nativity (self and parental), years lived in the U.S., and region of birth within the U.S., as previously reported (24). Language was categorized as English, Spanish, or Chinese. For participants native to the U.S., the number of years lived in the U.S. was determined by self-reported age.

Depressive symptoms were collected at baseline and most recently at Exam 5 using the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a 20-item self-report questionnaire designed to capture experiences of depressive symptoms over the past week on a four-point scale ranging from 0-3 and scores range from 0-60 (25).

Cardiometabolic Health Measures

We assessed several vascular health measures obtained at MESA Exam 6. Body mass index (BMI, kg/m^2) was calculated using participant's height and weight, and waist-to hip ratio was calculated by dividing the participant's waist circumference by hip circumference (centimeter/centimeter). Diabetes was classified as normal, impaired fasting glucose, untreated diabetes, and treated diabetes using the 2003 American Diabetes Association fasting criteria (100 to 125mg/dl) (26). Participant's general health was self-reported and measured on a 5-point Likert scale. Participants were asked, "Would you say, in general, your health is": 1, poor; 2, fair; 3, good; 4, very good; and 5, excellent. We collected information on both the total number of medications participants took (continuous) as well as whether they took medication for hypertension (yes/no). Metabolic syndrome was assessed using updated guidelines from the National Cholesterol Education Program (27).

Statistical Analysis

Chi Square tests were used to compare categorical variables and Kruskal Wallis tests were used to compare continuous variables. Multinomial logistic regression was used to investigate predictors of three patterns of ELA

Characteristic	ELA Refused (n=588)		ELA Partially Completed (n=75)		All ELA Completed (n=3174)		P-value
	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	
Age, yrs.		63.57 (9.70)		60.01 (9.37)		58.04 (8.57)	<0.001
Gender							0.61
Women	324 (55.10)		37 (49.33)		1748 (55.07)		
Men	264 (44.90)		38 (50.67)		1426 (44.93)		
Race and Ethnicity							<0.001
Black	162 (27.55)		16 (21.33)		822 (25.90)		
Chinese	133 (22.62)		9 (12.00)		355 (11.18)		
Hispanic/Latino	107 (18.20)		20 (26.67)		666 (20.98)		
White	186 (31.63)		30 (40.00)		1331 (41.93)		
Education							<0.001
<=HS	223 (37.93)		21 (28.00)		924 (29.11)		
Income							0.92
<75k	231 (39.29)		41 (54.67)		1723 (54.28)		
Language at Exam 1							<0.001
Chinese	117 (19.90)		7 (9.33)		274 (8.63)		
English	400 (68.03)		53 (70.67)		2596 (81.79)		
Spanish	71 (12.07)		15 (20.00)		304 (9.58)		
Years in the US		47.24 (22.75)		47.90 (20.32)		49.82 (17.53)	0.79
Region of Birth*							<0.001
South	168 (28.57)		18 (24.00)		941 (29.65)		
Midwest	71 (12.07)		15 (20.00)		810 (25.52)		
West	16 (2.72)		4 (5.33)		169 (5.32)		
Northeast	74 (12.59)		8 (10.67)		318 (10.02)		
Another country	255 (43.37)		30 (40.00)		924 (29.11)		
Missing	4 (0.68)				12 (0.38)		
Mother US Born	282 (47.96)		37 (49.33)		1991 (62.73)		<0.001
Father US Born	275 (46.77)		35 (46.67)		1938 (61.06)		<0.001
Investments							<0.001
No	234 (39.80)		25 (33.33)		924 (29.11)		
Yes	328 (55.78)		47 (62.67)		2145 (67.58)		
Missing	26 (4.42)		3 (4.00)		105 (3.31)		
Home Type							<0.001
Rent	169 (28.74)		22 (29.33)		744 (23.44)		
Mortgage	184 (31.29)		27 (36.00)		1415 (44.58)		
Own	170 (28.91)		18 (24.00)		843 (26.56)		
Other	39 (6.63)		5 (6.67)		71 (2.24)		
Missing	26 (4.42)		3 (4.00)		101 (3.18)		
Own Car							<0.001
No	141 (23.98)		12 (16.00)		390 (12.29)		
1 car	198 (33.67)		33 (44.00)		1122 (35.35)		
>1 car	226 (38.44)		27 (36.00)		1561 (49.18)		

Table 1. Baseline Sample Characteristics (2000-2002) by Response Pattern on Questions of Exposure to Early Life Adversity in the Multi-Ethnic Study of Atherosclerosis

Missing	23 (3.91)		3 (4.00)		101 (3.18)	
Own Property/land						0.17
No	389 (66.16)		49 (65.33)		2053 (64.68)	
Yes	155 (26.36)		23 (30.67)		874 (27.54)	
Currently buying	17 (2.89)				141 (4.44)	
Missing	27 (4.59)		3 (4.00)		106 (3.34)	
Father's Education						0.89
<=HS	409 (69.56)		54 (72.00)		2246 (70.76)	
Mother's Education						0.10
<=HS	463 (78.74)		54 (72.00)		2427 (76.47)	
Exam 6 CASI		87.95 (8.23)		89.10 (6.46)		90.57 (6.77)	<0.001
CES-D		7.18 (7.43)		7.12 (7.02)		7.16 (7.14)	0.97
BMI (kg/m^2)		27.01 (5.29)		28.13 (5.41)		28.71 (5.56)	<0.001
Waist-to-Hip Ratio (cm/cm)		0.94 (0.07)		0.92 (0.08)		0.94 (0.08)	0.20
Diabetes							0.13
Missing	252 (42.86)		15 (20)		662 (20.86)	
Normal	176 (29.93)		26 (34.67)		1301 (40.99)	
Impaired fasting glucose	65 (11.05)		19 (25.33)		601 (18.94)	
Untreated diabetes	10 (1.7)		2 (2.67)		103 (3.25)	
Treated diabetes	85 (14.46)		13 (17.33)		507 (15.97)	
General Health							<0.001
Missing	221 (37.59)		14 (18.67)		559 (17.61)	
Excellent	31 (5.27)		9 (12)		310 (9.77)	
Very good	94 (15.99)		14 (18.67)		938 (29.55)	
Good	139 (23.64)		27 (36)		948 (29.87)	
Fair	91 (15.48)		10 (13.33)		384 (12.1)	
Poor	12 (2.04)		1 (1.33)		35 (1.1)	
Total Medications		7.20 (4.98)		6.79 (4.15)		7.17 (4.70)	0.89
Hypertension							0.49
Missing	223 (37.93)		14 (18.67)		567 (17.86)	
No	112 (19.05)		19 (25.33)		878 (27.66)	
Yes	253 (43.03)		42 (56)		1729 (54.47)	
Metabolic Syndrome							0.15
Missing	275 (46.77)		18 (24)		724 (22.81)	
No	208 (35.37)		36 (48)		1489 (46.91)	
Yes	105 (17.86)		21 (28)		961 (30.28)	

Abbreviations: BMI, body mass index; CASI, Cognitive Abilities Screening Instrument; CES-D, Center for Epidemiologic Studies Depression Scale; cm, centimeter; CVD, cardiovascular disease; HS, high school; kg/m^2, kilograms/meters squared; N, number; SD, standard deviation; U.S., United States; yrs., years; *Participants born in Puerto Rico are grouped with those born in another country because although Puerto Rico is part of the U.S., differences in language, culture, and resources in Puerto Rico make it more similar to other countries than any specific region of the U.S.

Table 1 (Continued). Baseline Sample Characteristics (2000-2002) by Response Pattern on Questions of Exposure to Early Life Adversity in the Multi-Ethnic Study of Atherosclerosis

response in individual models, each adjusting for age, gender, race and ethnicity, and level of education. Multiple linear regression was applied to assess cross-sectional associations between ELA completion group and global cognitive function at MESA Exam 6 and change from Exam 5 to Exam 6. Findings are reported in partially adjusted models which included age, gender, race and ethnicity, level of education, and language spoken at Exam 1. Fully adjusted models were additionally adjusted for income, years in the U.S., mother's birthplace, father's birthplace, investments, home type, car ownership, mother's education, and father's education. Because CES-D was not administered at Exam 6, we were unable to adjust for current depression. However, we performed sensitivity analyses by utilizing CES-D scores from Exam 5. Associations between ELA response pattern and cognition and cognitive decline after adjusting for depression are reported separately.

Results

Our sample consisted of 3,837 adults who participated in the 2018-2019 follow-up 20 telephone interview. The mean baseline age of participants included in the analyses was 58.9 years (standard deviation [SD]=9.0), 55% were women, and 26% Black, 13% Chinese, 21% Hispanic/Latino, and 40% were White. Table 1 displays the demographic characteristics of the sample by response pattern among various sociodemographic and acculturation factors. Age, race and ethnicity, education, language at Exam 1, region of birth, parental birthplace, certain measures of wealth (i.e., investments, home type, and car ownership), and CASI at Exam 6 were all significantly associated with ELA response pattern ($p<0.001$). We also found that BMI and self-rated general health were significantly associated with ELA responsiveness ($p<0.001$); however, no other cardiovascular health measures were significant.

In Table 2, results are presented in individual multinomial logistic regression models evaluating predictors of possible response patterns, ELA refused and ELA partially completed. The group of participants who were administered and fully completed the ELA assessment were used as the reference category in these analyses (i.e., "All ELA Completed"). Models were adjusted for age, gender, race and ethnicity, and level of education. Participants who had an income of <$75k were less likely to refuse the ELA assessment than ELA completers with an income >=75k (odds ratio [OR]=0.68, 95% confidence interval [CI]: 0.52-0.90). When compared to English speaking participants, Spanish speakers were more likely to: (1) refuse the ELA (OR=2.15, 95% CI: 1.38-3.36, or (2) partially complete (OR=4.20, 95% CI: 1.47-11.98) the ELA assessment than to fully complete it. Region of birth was significantly associated with response pattern, with those born in the Northeast or another country outside of the U.S being more likely to refuse the ELA assessment (OR=1.54, 95% CI: 1.11-2.12; OR=1.66, 95% CI: 1.18-2.33) compared to ELA completers born in the Southern region of the U.S. For a 1-year increase in the number of years spent living in the U.S., the odds of both ELA refusal and partial completion was 2.0% lower compared to those who were born in the U.S. and fully completed the assessment (OR=0.98, 95% CI: 0.97-0.99). The odds of ELA refusal differed by parental birthplace, with mothers born in Puerto Rico (OR=2.69, 95% CI: 1.50-4.80) or a country outside of the U.S. (OR=1.74, 95% CI: 1.33-2.28), and fathers born in Puerto Rico (OR=2.75, 95% CI: 1.53-4.94) or a country outside of the U.S. (OR=1.65, 95% CI: 1.26-2.16), being more likely to refuse ELA questions than to fully complete the ELA assessment compared to those who reported their parents were born in the U.S. Likewise, those who only partially completed the ELA assessment were more likely to have a mother (OR=2.09, 95% CI:1.13-3.84) or father (OR=2.19, 95% CI: 1.19-4.04) born in another country compared to full completers with a parent born in the U.S.

Participants who refused to complete the ELA assessment were found to have reported different levels of wealth compared to those who fully completed the assessment. Specifically, Table 2 revealed that those who refused the ELA assessment were more likely to report no investments when compared to those who reported investing and completed the ELA assessment (OR=1.26, 95% CI: 1.01-1.58). Additionally, they were more likely to report renting a home than completers who reported owning one (OR=1.51, 95% CI: 1.16-1.96), and they were also less likely to report owning a car in comparison to completers who reported owning 1 car (OR=1.95, 95% CI: 1.50-2.53).

Table 2 also presents associations between measures of cardiovascular health and ELA responsiveness. We found that those with a lower BMI were less likely to refuse ELA questions

Characteristic*		ELA Refused (n=588)	ELA Partially Completed (n=75)
	OR (LCL, UCL)	OR (LCL, UCL)	
Income	<75K	0.68 (0.52, 0.90)	0.93 (0.51, 1.68)
Exam 1 language	English	Ref	Ref
	Spanish	2.15 (1.38, 3.36)	4.20 (1.47, 11.98)
	Chinese	1.57 (0.86, 2.85)	1.06 (0.21, 5.27)
Region of Birth †	South	Ref	Ref
	Midwest	0.60 (0.43, 0.82)	0.91 (0.43, 1.91)
	West	0.63 (0.36, 1.12)	1.17 (0.37, 3.74)
	Northeast	1.54 (1.11, 2.12)	1.24 (0.52, 2.96)
	Another Country	1.66 (1.18, 2.33)	2.07 (0.93, 4.63)
	Missing	1.62 (0.41, 6.41)	
Years in the US		0.98 (0.97, 0.99)	0.98 (0.96, 0.99)
Mother's Birthplace	U.S.	Ref	Ref
	Puerto Rico	2.69 (1.50, 4.80)	0.59 (0.07, 4.76)
	Another Country	1.74 (1.33, 2.28)	2.09 (1.13, 3.84)
	Missing	0.76 (0.10, 5.88)	
Father's Birthplace	U.S.	Ref	Ref
	Puerto Rico	2.75 (1.53, 4.94)	0.66 (0.08, 5.40)
	Another Country	1.65 (1.26, 2.16)	2.19 (1.19, 4.04)
	Missing	0.45 (0.06, 3.38)	
Investments	Yes	Ref	Ref
	No	1.26 (1.01, 1.58)	1.21 (0.68, 2.15)
	Missing	1.34 (0.84, 2.16)	1.37 (0.41, 4.54)
Home Type	Own	Ref	Ref
	Rent	1.51 (1.16, 1.96)	1.66 (0.83, 3.31)
	Mortgage	1.01 (0.79, 1.29)	1.07 (0.57, 2.02)
	Other	2.73 (1.71, 4.35)	3.74 (1.31, 10.69)
	Missing	1.51 (0.92, 2.46)	1.67 (0.48, 5.89)
Own Car	1 car	Ref	Ref
	No	1.95 (1.50, 2.53)	1.04 (0.53, 2.07)
	> 1 car	0.94 (0.76, 1.17)	0.59 (0.35, 0.10)
	Missing	1.25 (0.76, 2.07)	1.06 (0.32, 3.53)
Own Property/land			
	Yes	Ref	Ref
	No	0.99 (0.80, 1.23)	0.91 (0.54, 1.52)
	Currently Buying	0.88 (0.51, 1.51)	
Parental Education	>HS (mother)	Ref	Ref
	<=HS (mother)	0.91 (0.70, 1.18)	0.73 (0.40, 1.33)
	>HS (father)	Ref	Ref
	<=HS (father)	0.84 (0.67, 1.06)	1.11 (0.61, 2.03)

Table 2. Multinomial Logistic Regression for Predictors of ELA Response Patterns in MESA

BMI (kg/m^2)		0.97 (0.95, 0.99)	1.00 (0.95, 1.05)
Waist-to-Hip Ratio (cm/cm)		0.14 (0.03, 0.79)	0.01 (<0.001, 0.39)
Diabetes	Missing	2.22 (1.77, 2.78)	1.08 (0.56, 2.07)
	Normal	Ref	Ref
	Impaired Fasting Glucose	0.74 (0.55, 1.01)	1.52 (0.83, 2.79)
	Untreated Diabetes	0.63 (0.32, 1.24)	0.90 (0.21, 3.87)
	Treated Diabetes	1.15 (0.86, 1.54)	1.24 (0.62, 2.46)
General Health	Missing	2.82 (1.87, 4.27)	0.85 (0.36, 2.02)
	Excellent	Ref	Ref
	Very Good	0.93 (0.60, 1.43)	0.52 (0.22, 1.23)
	Good	1.22 (0.80, 1.85)	0.99 (0.45, 2.17)
	Fair	1.62 (1.02, 2.56)	0.89 (0.34, 2.32)
	Poor	2.17 (0.99, 4.75)	0.89 (0.11, 7.41)
Total Medications		0.99 (0.97, 1.02)	097 (0.92, 1.03)
Hypertension			
	Missing	2.10 (1.61, 2.75)	1.06 (0.52, 2.18)
	No	Ref	Ref
	Yes	0.84 (0.65, 1.08)	1.04 (0.59, 1.83)
Metabolic Syndrome	Missing	2.20 (1.78, 2.72)	0.98 (0.55, 1.76)
	No	Ref	Ref
	Yes	0.79 (0.61, 1.02)	0.90 (0.52, 1.56)

Abbreviations: BMI, body mass index; cm, centimeter; CVD, cardiovascular disease; ELA, early life adversity; HS, high school; kg/m^2, kilograms/meters squared; LCL, lower confidence interval; MESA, Multi-Ethnic Study of Atherosclerosis; OR, odds ratio; ref, reference; UCL, upper confidence limit; U.S., United States; *Separate models for each characteristic were adjusted for age, gender, race and ethnicity, and level of education. Outcome groups are compared to those who fully completed ELA. †Participants born in Puerto Rico are grouped with those born in another country because although Puerto Rico is part of the U.S., differences in language, culture, and resources in Puerto Rico make it more similar to other countries than any specific region of the U.S.

Table 2 (Continued). Multinomial Logistic Regression for Predictors of ELA Response Patterns in MESA

compared to those who completed the assessment (OR=0.97, 95% CI: 0.95-0.99). We also found that participants with a lower waist-to-hip ratio were less likely to refuse (OR=0.14, 95% CI: 0.03-0.79) or to partially complete (OR=0.01, 95% CI: <0.001-0.39) the ELA assessment compared to full completers. These results suggest that participants with higher BMI and greater waist-to-hip ratio were often more likely to refuse ELA questions. It is important to note that clinical variables indicating diabetes, general health, hypertension, and metabolic syndrome had a significant number of participants with missing data, particularly among those who also refused to complete the ELA assessment.

The associations between cognitive function at Exam 5 and Exam 6, and ELA response pattern are shown in Table 3. Model 1 was adjusted for age, gender, race and ethnicity, level of education, and language spoken at Exam 1. Fully adjusted models (Model 2) were adjusted for Model 1 covariates plus income, years in the U.S., mother's birthplace, father's birthplace, investments, home type, car ownership, mother's education, and father's education. Results from analyses of predictors of change in CASI score from Exam 5 to Exam 6 show no significant findings. Fully adjusted analyses of predictors of CASI scores at Exam 6 showed that there was no significant difference between participants who completed the full ELA assessment and those who refused the ELA assessment (beta=-0.68, standard error [SE] 0.49, p=0.168). Similarly, CASI scores at Exam 6 were not significantly different between full ELA completers and partial ELA completers (beta=0.08, [SE] 1.01, p=0.934) in Model 2. In sensitivity analyses, we added an indicator for depressive symptoms (Supplemental Table 2) and the associations between ELA response pattern and cognition were relatively unchanged.

	Change in CASI from Exam 5 to Exam 6 N=1539						CASI at Exam 6 N=1539					
	Model 1*			Model 2†			Model 1			Model 2		
ELA Response	β	SE	P-value	β	SE	P-value	β	SE	P-value	β	SE	P-value
ELA Refused	-0.48	0.54	0.37	-0.38	0.54	0.49	-0.90	0.50	0.07	-0.68	0.49	0.17
ELA Partially Completed	1.49	1.10	0.17	1.41	1.11	0.20	-0.02	1.02	0.99	0.08	1.01	0.93
All ELA Completed	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref

Abbreviations: β, beta; CASI, Cognitive Abilities Screening Instrument; ELA, early life adversity; MESA, Multi-Ethnic Study of Atherosclerosis; ref, reference; SE, standard error; *Model 1 adjusted for age, gender, race and ethnicity, level of education, and language spoken at Exam 1; †Model 2 adjusted for age, gender, race and ethnicity, level of education, language spoken at Exam 1, income, years in the U.S., mother's birthplace, father's birthplace, investments, home type, car ownership, mother's education, and father's education.

Table 3. Associations between ELA Response Pattern and Cognitive Change & Performance in MESA, 2010-2019

Discussion

Nonresponse has clear implications for the representativeness of study findings, and the reasons for nonresponse, or response bias, in research settings are considerable. Given the complex factors contributing to childhood adversity and maltreatment, it is particularly critical to evaluate representativeness when assessing such data. Research on the correlates of participant responsiveness typically focuses on sociodemographic characteristics and information related to the sample population (28). Demographic characteristics of MESA participants by ELA response pattern indicated significant associations for age, race and ethnicity, and education. Similarly, we found that specific factors associated with acculturation, including language spoken at Exam 1 and nativity at both the individual and parental level, were significantly associated with ELA completion status. MESA participants who spoke Spanish at Exam 1 were more likely than English speakers to have either refused or to have partially completed the ELA assessment, instead of fully completing the assessment. Likewise, foreign-born participants and participants with one or both parents born outside of the US, were more likely to either partially complete the ELA assessment or refuse it altogether.

Varying definitions of ELA, sampling biases, and the overall sensitivity of questions related to ELA can all contribute to a misrepresentation in the prevalence of childhood adversity (14). Similar to the issues of obtaining accurate and reliable information from retrospective reporting on childhood adversity, studies have observed differential response patterns in populations with poor cognitive performance and low SES (29, 30).

MESA's prospective cohort design, objective and longitudinal cognitive data collection, and diverse multi-ethnic and multi-lingual populations from 6 regions of the U.S. are among the advantages of this study. One of the major limitations of this paper is that cognitive data were not collected concurrently with the ELA questionnaire, and global cognitive assessments only occurred at Exam 5 and Exam 6. In addition, in-person cognitive testing may have offered a different level of participant engagement compared to the follow-up 20 telephone interview (which included the ELA questionnaire). The proportion of the sample that responded in an incomplete pattern was relatively small and may have limited our ability to detect significant group differences. Another limitation we encountered was that depression was collected at Exam 5 only. Importantly, because both ELA and cognition were collected long into MESA follow-up, there may be additional limitations due to general loss to follow-up. Regardless of these limitations, these findings contribute to new avenues in our understanding of the prevalence of childhood adversity, and the potential implications for later life cognition.

Conclusion

Our analyses underscore the value of considering response bias when interpreting research findings. The present study also illustrates the importance of assessing sample characteristics (e.g., gender, level of education, SES, etc.) associated with responsiveness when considering missing data. Moving forward, it will be beneficial to collect more longitudinal data targeting associations of exposure to ELA, responsiveness, and later life health outcomes. Establishing appropriate methods to assess exposure to ELA or any significant event(s) that take place before age 18, may impact health from a life course perspective; however, these data need to be further evaluated for response biases before any interpretation can be made.

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Ethical standards
The study was reviewed and approved by Institutional Review Boards at participating institutions. All participants provided informed consent for participation.

Conflict of interest
The authors report no conflicts of interest.

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