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Association of Early-Life Trauma and Risk of Adverse Cardiovascular Outcomes in Young and Middle-aged Individuals With a History of Myocardial Infarction

Zakaria Almuwaqqat, MD, MPH; Matthew Wittbrodt, PhD; An Young, MD, MPH; Bruno B. Lima, MD, PhD; Muhammad Hammadah, MD; Mariana Garcia, MD; Lisa Elon, MS, MPH; Bradley Pearce, PhD; Yingtian Hu, BS; Samaah Sullivan, PhD; Puja K. Mehta, MD; Emily Driggers, MPH; Ye Ji Kim, MPH; Tene` T. Lewis, PhD; Shakira F. Suglia, ScD, MS; Amit J. Shah, MD, MSCR; J. Douglas Bremner, MD; Arshed A. Quyyumi, MD; Viola Vaccarino, MD, PhD

IMPORTANCE Compared with older patients, young adults with a history of myocardial infarction (MI) tend to have a higher burden of psychosocial adversity. Exposure to early-life stressors may contribute to the risk of adverse outcomes in this patient population, potentially through inflammatory pathways.

OBJECTIVE To investigate the association of early-life trauma with adverse events and examine whether inflammation plays a role.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included patients aged 18 to 60 years with a verified history of MI in the past 8 months from a university-affiliated hospital network. Baseline data were collected from June 2011 to March 2016, and follow-up data were obtained through July 2019. Analysis began September 2019.

EXPOSURES Early-life trauma was assessed using the Early Trauma Inventory–Self Report short form (ETI-SR-SF), both as a continuous and as a binary variable at the threshold of a score of 7 or higher. Inflammatory biomarkers, interleukin 6, and C-reactive protein were obtained at baseline.

MAIN OUTCOMES AND MEASURES A composite end point of recurrent MI, stroke, heart failure hospitalization, and cardiovascular death over a median 3-year follow-up.

RESULTS Of 300 patients, the mean (SD) age was 51 (7) years, 198 (66%) were African American, and 150 (50%) were women. Compared with participants with MI with an ETI-SR-SF score less than 7, those with a score of 7 or higher had higher levels of interleukin 6 and C-reactive protein at baseline. Compared with participants with an ETI-SR-SF score less than 7, those with a score of 7 or higher were at a greater risk for adverse outcomes, with a hazards ratio of 2.3 (95% CI, 1.3-3.9). Results remained consistent in multivariable analysis. Further adjustment for C-reactive protein rendered the results no longer statistically significant. Early-life trauma displayed a dose-dependent response when analyzed as a continuous variable and by quartiles.

CONCLUSIONS AND RELEVANCE Early-life trauma is an independent risk factor for adverse outcomes in young and middle-aged individuals with a history of MI. Neurobiological mechanisms leading to lifetime activation of systemic inflammatory cascades may be implicated.

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Supplemental content

Author Affiliations: Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia (Almuwaqqat, Young, Lima, Hammadah, Garcia, Mehta, Shah, Quyyumi, Vaccarino); Rollins School of Public Health, Department of Epidemiology, Emory University, Atlanta, Georgia (Almuwaqqat, Young, Garcia, Pearce, Sullivan, Driggers, Kim, Lewis, Suglia, Shah, Vaccarino); Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia (Wittbrodt, Bremner); Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, Georgia (Elon, Hu); Atlanta VA Medical Center, Decatur, Georgia (Shah, Bremner).

Corresponding Author: Viola Vaccarino, MD, PhD, Rollins School of Public Health, Department of Epidemiology, Emory University, 1518 Clifton Rd NE, Room 3011, Atlanta, GA 30322 (viola.vaccarino@emory.edu).

Early-life trauma, occurring before age 18 years, has been linked to increased cardiovascular disease risk.[1] This effect may occur through neuroendocrine changes that increase vulnerability to depression and associated unhealthy behaviors[2] as well as through enduring inflammation.[3]

Young and middle-aged individuals with a history of acute myocardial infarction (MI), especially women and other marginalized individuals, tend to have an elevated burden of psychosocial adversity.[4] Thus, exposure to early-life trauma could contribute to the risk of adverse outcomes in these patients, potentially through inflammation. However, this question has not been explored before, to our knowledge.

In a sample of young and middle-aged individuals with a history of MI with a large representation of women and other marginalized individuals, we investigated whether early-life trauma is associated with the risk of adverse cardiovascular outcomes and whether systemic inflammation plays a role.

Key Points

Question Among individuals with a history of acute myocardial infarction, are those who had a past exposure to adverse childhood experiences at higher risk of adverse outcomes than those without such exposure?

Findings In this cohort study of 300 individuals with a history of myocardial infarction and exposure to higher levels of early-life trauma, there was a 2-fold increased incidence of adverse cardiovascular outcomes compared with those with lower exposure. The association was independent of other risk factors and was dose dependent.

Meaning Individuals with a history of myocardial infarction and early-life trauma may be at increased long-term risk of adverse cardiovascular outcomes.

Methods

Between June 2011 and March 2016, the Myocardial Infarction and Mental Stress 2 study enrolled adults aged 18 to 60 years with a documented history of MI in the previous 8 months from Emory University-affiliated hospitals in Atlanta, Georgia.[5] The diagnosis of MI (type 1) was verified based on standard criteria,[6] and recruitment was balanced by sex by enrolling all consecutive eligible women and a subsample of men. Early-life trauma was assessed using the Early Trauma Inventory-Self Report short form (ETI-SR-SF), a validated 27-item instrument for the assessment of trauma incurred before age 18 years (eAppendix in the Supplement).[7,8] C-reactive protein (CRP) and interleukin 6 levels were measured at baseline. The Beck Depression Inventory and posttraumatic stress disorder symptoms scales were administered.[9,10] Details for other measurements have been published.[5] Participants were followed up for a median of 3 years for the study end point (a composite of cardiovascular death, MI, stroke, or hospitalization for heart failure) through patient contacts, medical record review, and the Social Security Death Index. Cardiovascular death included fatal MI, fatal stroke, or death due to cardiac arrhythmia or heart failure. All events were adjudicated by study cardiologists blinded to other study data. The research protocol was approved by the Emory University institutional review board and all participants provided informed consent.

The ETI-SR-SF total score (range, 0 to 27) was analyzed as a continuous variable (per 4-point increase) and as a categorical variable, using a cut point of 7.[8] Linear regression was used to examine the association between the ETI-SR-SF score and CRP/interleukin 6 levels. Cox proportional hazard regression was used to derive hazards ratios and 95% CIs for the association between ETI-SR-SF score and the study end point before and after adjustment for other patient characteristics. We adjusted for the natural log of CRP in our final model. To illustrate the results, we constructed Kaplan-Meier survival curves of event-free survival using ETI-SR-SF score quartiles. Two-sided *P* values had a significance threshold of .05. SAS software version 9.4 (SAS Institute) was used for analysis. Analysis began September 2019.

Results

From 313 participants enrolled, we excluded 13 individuals who did not complete the ETI-SR-SF, leaving 300 participants in the analytical sample. Of these, follow-up data were available for 297 patients. The mean (SD) age was 51 (7) years, 198 (66%) were African American, and 150 (50%) were women. Overall, 154 individuals (51%) reported early-life trauma, defined as an ETI-SR-SF score of 7 or higher. Participants with an ETI-SR-SF score of 7 or higher, compared with those with an ETI-SR-SF score less than 7, were more likely to be Black or African American and had a more adverse socioeconomic, psychosocial, and cardiometabolic profile (**Table 1**). Moreover, those with an ETI-SR-SF score of 7 or higher had higher baseline levels of interleukin 6 and CRP independent of demographic and clinical risk factors as well as depression and posttraumatic stress disorder symptoms (eTable in the Supplement).

Over a 3-year follow-up, 59 outcome events for the composite end point were ascertained. Compared with participants with an ETI-SR-SF score less than 7, those with a score of 7 or higher had a 2-fold incidence of the study end point (40 [26%] vs 19 [13%]; $P = .004$). All event types were more frequent among participants with an ETI-SR-SF score of 7 or higher than those with a score less than 7 (**Figure** A).

Using Cox proportional hazard models (**Table 2**), a 4-point increment in the ETI-SR-SF score was associated with a 30% higher hazard of the composite outcome (95% CI, 10%-50%). The association was only slightly attenuated after adjustment for demographic and clinical factors. Further adjustment for posttraumatic stress disorder and depression did not substantially change the results. Results were consistent for ETI-SR-SF score as a binary variable (Table 2). The unadjusted hazard for the composite end point was more than 2-fold higher in those with ETI-SR-SF score of 7 or higher than those with ETI-SR-SF scores less than 7 (hazard ratio, 2.3; 95% CI, 1.3-3.9) and remained elevated after adjustment for the same covariates. However, after adding CRP, the association was no

Table 1. Baseline Characteristics of the Cohort by ETI-SR-SF Score Cutoff of 7 (N = 300)

Characteristic	ETI-SR-SF score, No. (%)		*P* value
	<7	≥7	
No.	146	154	NA
Demographic factors			
Age, mean (SD), y	51 (7)	51 (7)	.51
Female	76 (52)	74 (48)	.50
African American	87 (60)	111 (72)	.02
Education >12 y	96 (66)	82 (53)	.03
Household income <$25 000	39 (29)	72 (52)	.001
Married or living with partner	73 (50)	52 (34)	.004
Psychosocial factors, median (IQR)[a]			
PTSD symptom checklist	22 (20-29)	32 (24-48)	.001
Beck Depression Inventory II	6 (3-11)	15 (6-24)	.001
Clinical factors			
Hypertension	112 (77)	132 (86)	.053
Diabetes	35 (24)	58 (38)	.12
Obesity, BMI ≥30	63 (43)	155 (60)	.004
Dyslipidemia	116 (80)	125 (81)	.71
Ever smoker	61 (42)	103 (67)	<.001
CAD (stenosis ≥70%)	120 (88)	117 (82)	.23
Ejection fraction, median (IQR)[a]	55 (48-60)	53 (45-60)	.06
Medications			
β-Blockers	127 (87)	130 (85)	.61
Aspirin	123 (84)	129 (79)	.32
ACE inhibitors	56 (39)	84 (55)	.008
Statins	125 (86)	129 (84)	.82

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; ETI-SR-SF, Early Trauma Inventory–Self Report short form; IQR, interquartile range; NA, not applicable; PTSD, posttraumatic stress disorder.

[a] Nonparametric testing.

longer statistically significant. When we examined ETI-SR-SF quartiles, a dose-dependent association emerged (Figure B).

Discussion

In this study of young and middle-aged adults with a recent MI, early-life adversity, as measured by the ETI-SR-SF, was a common exposure and was associated with a substantial increase in risk. High levels of early-life adversity as a categorical variable were associated with approximately a doubling of the risk for adverse cardiovascular outcomes. There was a gradation of effect. Each 4-point increase in the ETI-SR-SF score was associated with a 20% increased risk for the study end point after adjusting for demographic and cardiovascular risk factors, and individuals in the highest exposure quartile showed more than 4-fold increased risk compared with the lowest quartile.

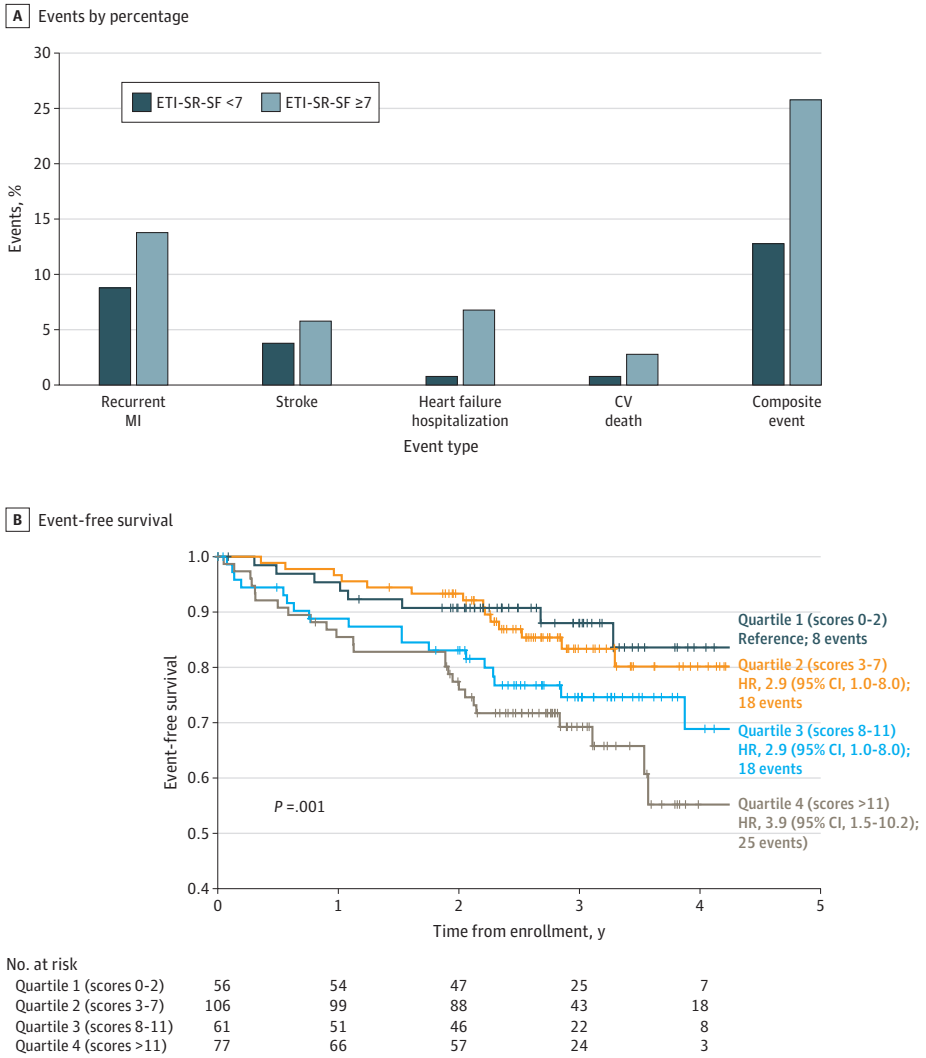
While patients with MI who reported higher levels of early-life adversity had a greater burden of psychosocial and cardiovascular risk factors, the association of early-life trauma with adverse outcomes was independent of these factors. However, the association was no longer statistically significant after adjustment for baseline inflammation. These results suggest that adverse childhood experiences contribute to cardiovascular risk after an MI in part through a pathway that involves inflammation,[11] an association possibly due to decreased glucocorticoid signaling with downstream upregulation of the inflammatory cascade.[11,12]

To our knowledge, this study is the first to describe an excess risk of adverse outcomes in patients with previous MI who report early-life adversity. Prospective studies have indicated that reports of such exposures predict future cardiometabolic health in general population samples.[13-15] Our study adds new evidence to show that among young and middle-aged patients with a history of MI, early-life adversity is a powerful predictor of subsequent clinical events. Urban patient populations with early-onset MI could be especially vulnerable toward the enduring effects of early-life adversity.[1]

Limitations and Strengths

A limitation of this study is the retrospective assessment of early trauma. However, outcomes were assessed prospectively; thus, any potential misclassification of trauma exposure is likely nondifferential, which would bias the results toward the null. Our cohort included a sample of limited size from a single city and lacked data from patients with MI older than 60 years. While this can be a limitation, the high proportion of younger African American individuals and women in our sample is a strength because these groups are underrepresented in studies of cardiovascular disease. Our research addresses an understudied, high-risk population with a large psychosocial burden, among whom the enduring influences of early stressful exposures could be especially deleterious.

Figure. Cardiovascular (CV) Outcomes Associated With Early-Life Trauma



A, Frequency of CV outcomes in participants with Early Trauma Inventory–Self Report short form (ETI-SR-SF) score less than 7 and 7 or more. *P* = .004 comparing the frequency of the composite end point between patients with ETI-SR-SF score less than 7 and those with ETI-SR-SF score of 7 or more. B, Kaplan-Meier survival curves for event-free survival after myocardial infarction by quartiles of ETI-SR-SF. Adverse CV events were defined as CV death, myocardial infarction (MI), stroke, or hospitalization for heart failure. *P* value from log-rank test = .001 (n = 297). HR indicates hazard ratio.

Table 2. Multivariable Cox Regression Analysis of the Association Between ETI-SR-SF Score and the Study End Point (n = 297)

Continuous variable	Per 4-point increase in ETI-SR-SF score, HR (95% CI)
Unadjusted	1.3 (1.1-1.5)
Adjusted for demographic factors[a]	1.2 (1.0-1.4)
Adjusted for above variables plus cardiovascular risk factors and medications[b]	1.2 (1.0-1.4)
Adjusted for above variables plus PTSD and depressive symptoms	1.2 (1.1-1.5)
Adjusted for above variables plus lnCRP[c]	1.2 (0.99-1.5)
Binary variable	**Total ETI-SR-SF score ≥7 vs <7, HR (95% CI)**
Unadjusted	1.3 (1.1-1.5)
Adjusted for demographic factors[a]	1.2 (1.0-1.4)
Adjusted for above variables plus cardiovascular risk factors and medications[b]	1.2 (1.0-1.4)
Adjusted for above variables plus PTSD and depressive symptoms	1.2 (1.1-1.5)
Adjusted for above variables plus lnCRP[c]	1.2 (0.99-1.5)

Abbreviations: ETI-SR-SF, Early Trauma Inventory Self Report–short form; HR, hazard ratio; PTSD, posttraumatic stress disorder; lnCRP, natural log of C-reactive protein.

[a] Age, sex, race (Black vs non-Black), and education (>12 years).

[b] History of hypertension, diabetes mellitus, body mass index, ever smoking, ejection fraction, statin and aspirin use.

[c] Because of missing values, the sample in this model is 262 patients.

Conclusions

In conclusion, young and middle-aged individuals with a history of MI and early-life trauma are at higher risk for adverse cardiovascular outcomes than those with fewer or no similar experiences. Our research reveals that exposure to early-life adversity is an important prognostic indicator in this group, potentially through a proinflammatory state.

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Concept and design: Almuwaqqat, Hammadah, Shah, Bremner, Vaccarino.
Acquisition, analysis, or interpretation of data: Almuwaqqat, Wittbrodt, Young, Lima, Garcia, Elon, Pearce, Hu, Sullivan, Mehta, Driggers, Kim, Lewis, Suglia, Shah, Bremner, Quyyumi, Vaccarino.
Drafting of the manuscript: Almuwaqqat, Bremner, Vaccarino.
Critical revision of the manuscript for important intellectual content: All authors.
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