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ABSTRACT

Background: Childhood adversity (CA) is linked to suicidal behavior as well as to mood disorders and aggressive traits. This raises the possibility that depression and aggressive traits mediate the relationship of childhood adversity to suicide risk. Moreover, it is not known if they operate independently or interactively.

Aims: To determine whether, and how, mood disorders and aggressive traits mediate the effects of reported physical and sexual abuse on future suicidal behavior.

Methods: Five hundred and forty-eight subjects, offspring of parents with mood disorders, were interviewed at baseline and at yearly follow-ups with questionnaires assessing aggression, mood disorders, and suicidal behavior. The mediation analysis involved a three-step process, testing the relationships between (1) CA and attempt; (2) CA and putative mediators; and (3) putative mediators and suicide attempt, adjusting for CA.

Results: Aggressive trait severity and mood disorder onset each mediated the relationship between CA and future suicide attempts. Greater aggression severity also raised the hazard of the development of a mood disorder. If aggressive trait severity was clearly elevated, then onset of mood disorder did not increase further the hazard of the suicide attempt. Including family as a random effect had a much bigger effect on attempt outcome for physical abuse compared with sexual abuse.

Conclusions: Amelioration of aggressive traits and treatment of mood disorders in CA-exposed offspring of a parent with a mood disorder may prevent future suicide attempts and may reduce the risk of mood disorder. Familial factors influence the impact of childhood physical abuse but not sexual abuse.

KEYWORDS

Aggression; child and adolescent psychiatry; childhood adversity; mood disorder; suicide

HIGHLIGHTS

- Childhood Adversity (CA) predicted future mood disorder and aggression severity.
- Depression and aggression mediate the relationship between CA and suicide attempts.
- When one mediator is present, the presence of the other does not increase the hazard.

*These authors share first authorship.

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- Between family variation contributed much more to suicidal behavior outcomes relative to the effect of physical abuse, but sexual abuse contributed to suicidal outcomes more than family variation.

INTRODUCTION

Suicide is a major cause of death in the United States (Control, 2020) where the suicide rate rise annually from 2000 to 2019. The risk for suicidal behavior is transmitted in families (Brent et al., 2002; Melhem et al., 2019) and has moderate heritability that motivates active efforts to identify candidate genes that may be responsible (Mullins et al., 2014; Statham et al., 1998). Even genetic causal pathways leading to suicide are potentially modifiable for prevention purposes if one can identify the related phenotypes. Clarifying relationships between variables that comprise modifiable causal pathways may enhance suicidal behavior prevention.

Childhood adversity (CA) can include reported physical and sexual abuse, parental divorce, emotional neglect, deprivation, and exposure to domestic violence, and is a major risk factor for suicidal behavior (Brodsky & Stanley, 2008; Franklin et al., 2017; Miller et al., 2017). A key question is what are potential mediators of the relationship between childhood adversity and suicidal behavior? If the mediators are modifiable, then suicidal behavior related to childhood adversity may be preventable through targeted intervention.

One potential mediator of the relationship between CA and suicidal behavior is a mood disorder. CA increases the risk for developing mood disorders, and other psychopathologies that also carry an increased risk of suicidal behavior, such as antisocial personality disorder and post-traumatic stress disorder, as well as medical diseases, such as cardiovascular disease, cancer, and chronic pain (Appleton, Holdsworth, Ryan, & Tracy, 2017; Björkenstam, Vinnerljung, & Hjern, 2017; Corcoran & McNulty, 2018; Felitti et al., 2019; Harford, Yi, & Grant, 2014; Holman et al., 2016; Hughes et al., 2017; Infurna et al., 2016; Lippard & Nemeroff, 2020; Liu, 2017; Mall et al., 2018; Mandelli, Carli, Roy, Serretti, & Sarchiapone, 2011; Mandelli, Petrelli, & Serretti, 2015; Merrick et al., 2017; Schalinski et al., 2016; Schilling, Aseltine, & Gore, 2008; Suglia et al., 2018; Wainwright & Surtees, 2002; You, Albu, Lisenbardt, & Meagher, 2019). Mood disorders are the commonest psychopathologies associated with suicidal behavior (Dong et al., 2018; John Mann et al., 2016; Kandel, Raveis, & Davies, 1991; Keilp et al., 2012; Miller et al., 2017; Rentería et al., 2017; Ribeiro, Huang, Fox, & Franklin, 2018; Tondo & Baldessarini, 2016). About nine in ten suicide decedents have a comorbid psychiatric disorder at the time of death. A major depressive episode is the most common of these psychiatric disorders (Hawton, i Comabella, Haw, & Saunders, 2013). One heuristic model, the diathesis-stress model of suicidal behavior (Mann & Rizk, 2020), proposes that exposure to childhood adversity may lower the threshold for stress needed to cause a future depressive reaction (Hammen, Henry, & Daley, 2000) or make a suicide attempt (Leon, Friedman, Sweeney, Brown, & Mann, 1990). Therefore, mood disorders have the potential to mediate the relationship between CA and suicidal behavior.

CA is also related to the development of aggressive traits (Matsuura, Hashimoto, & Toichi, 2009). CA predicts greater verbal and physical aggression later in life (Mumford, Taylor, Berg, Liu, & Miesfeld, 2019). Adverse social environments, including childhood maltreatment, maternal antisocial behavior, and family dysfunction, predict trait physical aggression (Campbell et al., 2010; Chartrand, Bhaskaran, Sareen, Katz, & Bolton, 2015; Nagin & Tremblay, 2001). Violent behaviors in childhood, adolescence, and adulthood are related to reported childhood maltreatment and adverse parenting experiences (Brodsky & Stanley, 2008; Chartrand et al., 2015; Duke, Pettingell, McMorris, & Borowsky, 2010; Hall, Stinson, & Moser, 2018; Kubiak, Fedock, Kim, & Bybee, 2017; Langton, Murad, & Humbert, 2017; Mumford et al., 2019; Stinson, Quinn, & Levenson, 2016; Vaughn, Salas-Wright, Underwood, & Gochez-Kerr, 2015). Like mood disorders, aggressive traits also increase the risk for suicidal behavior (Bridge et al., 2015; Coryell et al., 2018; Fite, Poquiz, Frazer, & Reiter, 2017; Franklin et al., 2017; Gvion, 2018; Keilp et al., 2006; Lewis, Meehan, Cain, & Wong, 2016; McCloskey & Ammerman, 2018; O'Rourke, Jamil, & Siddiqui, 2019; Tondo & Baldessarini, 2016; Turecki & Brent, 2016). Therefore, these traits, which can have genetic and epigenetic causes (Orri et al., 2020), have the potential to mediate the relationship between CA and suicidal behavior risk.

Despite a substantial body of research linking CA to suicidal behavior and these two potential mediators, very few studies to date were designed to test a possible mediation effect of mood disorders and aggressive traits on the relationship between CA and suicidal behavior. Moreover, previous work on mediators of the CA and suicide relationship has been limited in scope. Most published studies that have examined the connection between CA and suicidal behavior, and the relationship between depression and aggressive traits, have used a retrospective or cross-sectional design (Bridge et al., 2015; Gould et al., 1994; Keilp et al., 2012). A longitudinal design for a study of a mediation effect is crucial. A mediation analysis assumes that A can cause B because A appears before B in the life of the individual. No longitudinal study (Espejo et al., 2007; Provençal, Booij, & Tremblay, 2015; Tremblay et al., 2004) has examined the role of both major depressive episodes and aggressive behavioral traits in mediating the effect of childhood adversity on subsequent suicide behavior risk. Therefore, we do not know if these two components independently mediate the effect of CA on suicidal behavior, and we do not know if there is an interaction effect. We aimed to address these questions by utilizing a prospective design to investigate the potential mediational pathways between CA and suicidal behavior.

The present study employed a longitudinal design to examine the relationship of reported CA before 16 years of age to a subsequent mood disorder and too aggressive traits measured after age 16 years. We determined the relationship of these potential mediators, and their interaction, with suicidal behavior that was detected prospectively after that age. A mediation analysis was performed to determine whether the effects of reported CA on aggressive traits and mood disorders, separately and together, mediated the relationship of a reported history of physical and sexual CA to suicidal behavior. To establish mediation, if a mood disorder developed, it had to develop after the CA, but before the suicide attempt. Given that suicide is related to both mood disorders and aggressive traits, we hypothesized that each is a mediator of the effects of CA on suicidal behavior after the age of 16. We also explored the possibility of an interaction between mood disorders and aggressive traits.

MATERIALS AND METHODS

Sample

The sample population comprised 548 offspring of 294 parents with mood disorders, ages 16 years and older. All subjects were recruited from Western Psychiatric Institute and Clinic (Pittsburgh, PA, USA) or New York State Psychiatric Institute/Columbia University Medical Center (New York, NY, USA). One parent of each subject was a participant in our two-site study protocol examining familial transmission of mood disorders and suicidal behavior (Brent et al., 2002; Melhem et al., 2019). Half the parents also had a lifetime history of a suicide attempt. The current study examined *only the offspring* of these parents because the offspring had been followed longitudinally from as early as childhood into early and mid-adulthood.

This offspring population was at elevated risk for mood disorders and suicidal behavior because they all had a parent(s) with a mood disorder. A mood disorder was required for the recruitment of all parents in the previous protocol, and in fact, half of the parents had a history of a suicide attempt. Two hundred and twenty (75%) of the families had more than one offspring in the sample and 96 (33%) had more than two offspring. Table 1 displays demographic information for the study sample. The 548 offspring included 258 (47.1%) females. Offspring had a mean age of 20.3 years at baseline and 26.1 years at the last follow-up visit. One hundred and eighty-one out of the 240 subjects with known race (75%) were Caucasian and non-Hispanic, 40 out of the 240 (17%) non-Hispanic blacks, and 50 out of the 547 with known Hispanic ethnicity (9%). One hundred and ninety subjects (34.7%) were diagnosed with MDD and 35 (6.3%) with bipolar disorder. One hundred and sixty-six subjects, or 30.3% of the sample, had taken antidepressants before or during their participation in the study.

TABLE 1. Clinical and demographic descriptive data for study sample.

White, non-Hispanic	75.4% [2.8%], $n = 240$
Black, non-Hispanic	16.7% [2.4%], $n = 240$
Hispanic	9.1% [1.2%], $n = 548$
Age at baseline*	20.3 ± 8.9 years [0.40], range = 8.3–50.9, $n = 504$, median = 17.610
Age at last visit	26.07 ± 8.2 years [0.35], range = 16–57.9, $n = 547$, median = 24.0
History of physical abuse	16.3% [1.60%], $n = 533$
History of sexual abuse	11.0% [1.4%], $n = 535$
Length of follow up	6.5 ± 3.54 years [0.16], range = 0–13.6, $n = 503$, median = 7.04
Female sex	47.1% [2.1%], $n = 548$
Proportion making a suicide attempt at any point before or during study but none before age 16 years**	5.9% [1.0%], $n = 523$
Aggression at baseline (z-scores)	0.00 ± 1.0 [0.07], range = −1–3.9, $n = 203$
Aggression at last assessment (z-scores)	−0.01 ± 0.97 [0.046], range = −1–5.2, $n = 444$
Proportion of offspring observed to have had an onset of mood disorder at any age**	45.4% [2.1%], $n = 546$
Proportion of offspring observed to have had an onset of mood disorder after age 16 years**	31.6% [1.8%], $n = 546$

Means, [SE], *n*, and (where applicable) ± *SD* and range of subjects having non-missing data. (SD's and SE's calculated using naive formula not taking into account possible family random effect).
*Some subjects were enrolled before age 16. Only their post-16 data were used in the analyses.
**Does not take into account censoring.

Assessment

The study protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute and Western Psychiatric Clinic, University of Pittsburgh Medical Center, respectively. Written informed consent was obtained from adult subjects and parental consent and assent were obtained for those <18 years old. Offspring were interviewed at baseline and yearly follow-up interviews. The median length of the follow-up period was 7.0 years, ranging from 0 to 13.6 years. Lifetime and current DSM-IV psychiatric disorders at baseline were ascertained using the Schedule for Affective Disorders and Schizophrenia for School-Age Children for offspring between the ages of 10 and 17 years, Present and Lifetime Version (KSADS-PL) (Kaufman et al., 1997), alpha coefficient of 0.869 and the Structured Clinical Interview for DSM-IV (SCID), alpha coefficient of >0.8 (Spitzer, Williams, Gibbon, & First, 1992) were used for subjects older than 18 years. Masters' level clinical interviewers conducted these interviews. A group of clinical research physicians and psychologists reviewed the data and reached a consensus regarding all diagnoses. Within- and cross-site reliability for SCID-I and KSADS-PL was high (Brodsky & Stanley, 2008).

Suicidal Behavior

Suicidal behavior (number of suicide attempts, lethality, intent) was assessed using the Columbia-Suicide History Form (Oquendo, Halberstam, & Mann, 2003) and the Scale of Suicide Ideation (Beck, Kovacs, & Weissman, 1979), alpha coefficient of 0.84–0.89 when administered by an experienced Masters level or Ph.D. interviewer. We used the Columbia definition for suicide attempts (Posner et al., 2008) and only events of self-harm with intent to die were counted as suicide attempts (Oquendo et al., 2003). Criteria for suicide attempts were verified at a consensus conference. Of the 548 offspring, 31 made at least one suicide attempt over the course of the study and after their 16th birthday. Analyses included only those subjects whose first suicide attempt came after 16 years of age, because the CA had to come before the suicide attempt to test a potential mediator.

Onset of Mood Disorder

For each subject, we determined the age of onset of mood disorder, if any, using the SCID and K-SAD and our baseline demographics and developmental history form. Since the patients in our sample had yearly follow-up appointments and during those follow-up appointments, they completed repeat SCID and K-SADs, we were able to pinpoint the age at which they developed a mood disorder based on those scales. Mood disorders included in the analyses were major depressive disorder, mania, hypomania, depressive disorder NOS, bipolar I, bipolar II, bipolar NOS, and mixed episode. Details on the sources for each diagnosis are available in the Supplementary Materials. Mood disorder onset was of significance to ensure that the mood disorder was present before the development of the suicidal behavior, thus making it a time-varying predictor. For this reason, to study mood onset as a mediator, Cox regression with time-varying predictors was employed (Therneau & Grambsch, 2000). Only subjects with no mood

disorder before the age of 16 years were included in analyses involving mood disorder because we needed cases where the CA preceded the onset of the mood disorder.

Aggression

The Brown Goodwin Lifetime History of Aggression (BGLHA) Scale (Brown & Goodwin, 1986), an 11-item rating scale, with an alpha coefficient of .76–.91, was used to assess the severity of aggressive behaviors. It should be noted that to ensure that we were measuring a stable trait reflecting the effects of CA, we only used ratings obtained after the age of 16 years. We used the adult component of the baseline BGLHA and all available follow-up adult BGLHA ratings. We also used the child scores for time points 16–18 years. For each item on the child Brown-Goodwin follow-up scale, there is the child's response, the parent's response, and a summary of the two. To combine the adult and child scores into a single variable, we converted these ratings of aggression after age 16 years to *z*-scores, separately for the adult and child. For each subject we used the mean score, over all available assessments, to create a single aggression value as a measure of aggressive trait severity for that subject. We call the resulting variable "BGz."

Childhood Adversity

We focused on physical and sexual abuse and not deprivation or emotional abuse because the former were more reliably and more completely ascertained. History of childhood abuse was assessed in this study sample using four distinct measures because not all measures were used in all subjects over the entire study period: Child Experiences Questionnaire (Bernstein et al., 1994), Child Trauma Questionnaire (Chaffin, Wherry, Newlin, Crutchfield, & Dykman, 1997), Childhood and Adolescence Review of Experiences (CARE) questionnaire (Harris & Renschler, 2015), and the Baseline Demographic and Developmental (BDEMO) History Form. The Child Experiences Questionnaire (CEQ) is a self-reported measure of child trauma in which subjects report on abuse up to the age of 15 years, with an alpha coefficient of 0.92. This measure demonstrated reliability for both physical and sexual abuse at initial assessment (Brent et al., 2002; Brodsky & Stanley, 2008). The Child Trauma Questionnaire (CTQ) is a self-reported measure consisting of 28 items to assess the severity of emotional abuse/neglect, physical abuse, and sexual abuse, with an alpha coefficient of 0.91. The CARE is an interview measure that retrospectively assesses the presence or absence of physical abuse and/or sexual abuse, age of onset, severity, duration, and perpetrator of abuse between ages 0 and 18 years. This interview measure is based on a self-report measure that has sound psychometric properties (Chaffin et al., 1997). The baseline demographics and developmental (BDEMO) history form, antedated the Abuse Dimensions inventory (Chaffin et al., 1997) and the CTQ. This form is administered by an interviewer and includes three yes/no questions related to physical and sexual abuse: (1) for any history of physical and/or sexual abuse over a lifetime: (2) if yes, was the abuse physical, sexual or both; and (3) if yes, did abuse take place before age 16 years? These screening questions have been used in our previous work to assess lifetime childhood abuse (Brodsky & Stanley, 2008).

We deemed a subject to have experienced sexual abuse before age 16 years if any of these instruments indicated they had. If at least one of the instruments indicated there was no history of sexual abuse (before age 16 years) then the variable was assigned the value "no abuse." If neither of these cases were obtained, the variable's value was designated as missing. The physical abuse variable was defined similarly.

The age cutoff of 16 years was chosen because the instruments employed, specifically, the BDEMO and CTQ, assessed history of childhood adversity before age 16 years without being more specific about timing.

Data Analysis

Mediation means there is a causal chain: abuse -> mediator(s) -> suicidal behavior, where "->" indicates causality. In addition, abuse might contribute directly to suicidal behavior. *Such a causal chain can only occur if the mediator appears after the abuse but before the suicidal behavior.*

The instruments employed, specifically the BDEMO and CTQ, assessed the history of childhood adversity before age 16 years without being more specific about timing. Because in general, we could only ascertain whether abuse occurred before age 16, we only considered mediation variables (aggression level and mood onset, if any) and outcome (suicide attempt) measured *after age 16*.

We used the adult component of the baseline BGLHA (18 years and up) and all available follow-up adult BGLHA ratings after baseline. If a subject entered the study before the age of 18 years, we used the child Brown-Goodwin follow-up scale to measure aggression traits between ages 16 and 18. For each item on, that scale there is the child's response, the parent's response, and a summary of the two. We used the summary, for data points 16–18 years. To combine the adult and child scores into a single variable, we converted these ratings of aggression after age 16 years to *z*-scores, separately for the adult and child scales. For each subject we used the mean score, over all available assessments (after age 16), to create a single aggression value as a measure of aggressive trait severity for that subject. We call the resulting variable "BGz."

Mood disorder onset was considered present only if it occurred before the first suicide attempt or the last follow-up visit whichever came first. Otherwise, it was considered absent. Since mood disorder may begin at any time in that interval it is a time-varying predictor. For this reason, to study mood onset as a mediator, Cox regression with time-varying predictors was employed (Therneau & Grambsch, 2000). Only subjects with no mood disorder before the age of 16 years were included in analyses involving mood disorder.

We establish mediation by performing three tests (Baron & Kenny, 1986; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002):

1. Test CA as a predictor of a suicide attempt. The rationale is that if childhood adversity does not increase risk, there is nothing to mediate.
2. Test CA as a predictor of the potential mediator(s). CA must be associated with the mediator, otherwise, CA does not causally affect the mediator.

3. Test separately and together and with an interaction term (because there are two mediators), whether the putative mediators are associated with suicide attempts after adjusting for CA (sexual and physical separately). The mediator must be associated with suicide attempts more than just by virtue of its association with CA.

The analysis testing relationship (1) for the effect of CA on suicide attempts only involved childhood physical or sexual adversity and not deprivation, based on having more complete active abuse data compared with deprivation data. In analyses testing relationships (1) and (2), we looked for a significant CA effect. However, in analyses testing relationship (3), only a significant mediator effect was of interest.

Mood onset and suicide attempt are "censored" events: The subjects may not experience these events up until their last follow-up. So whenever either of these events played the role of dependent variable we used survival analysis, specifically Cox regression (Therneau & Grambsch, 2000) because it allows for attrition, under the assumption that the attrition and suicide attempt processes are independent of each other. The "survival analysis clock" started at age 16 years and stopped either at the first suicide attempt or the last follow-up assessment (whichever came first).

For the type (2) analysis *CA -> aggression* we used linear regression. Because there may be between subjects or between family effects, in the linear and Cox regressions, we incorporated random effects. There are three choices for random effects: family, subject, or both. For some analyses, a subject effect was not applicable. We fitted models including each of these random effects that were relevant to the analysis and chose the model for which the BIC value was the smallest (Rao & Wu, 2001). Linear regression with random effects is just a standard mixed linear model (Gueorguieva & Krystal, 2004; Searle, Casella, & McCulloch, 2009). We fitted mixed Cox regression models using the R function coxme (Therneau, 2012).

In addition to conducting these tests, we estimated the effect of abuse history as filtered through its effect on BG. That is, we estimated the effect of CA on SA through the pathway $CA > aggression > attempt$. The first step was to multiply the coefficient estimate in the type 2 analysis, $abuse > BGz$, by the coefficient of BGz in the type 3 analysis, $abuse + BGz > attempt$, then exponentiate the product to get the hazard ratio. We computed a bootstrap percentile confidence interval for this product by a non-parametric bootstrap using 15,000 resamples. We did this separately for physical and sexual abuse. Such a calculation is not possible for mood onset because, though CA might heighten the risk of mood disorder, the onset of a mood disorder may not occur until after the suicide attempt.

To test the proportional hazards assumption, we fitted Cox regression models, including interactions between predictor variables and various functions of time (Rosenberg, 2011). See Supplementary Material for details.

In linear regression, including linear mixed models, one can compute the proportion of variance explained by a fixed or random effect. We report a result of this sort of aggression.

Now, in Cox regression, the notion of "variance" does not make sense. One cannot speak of the "percent of variance explained by family" in a mixed-effects Cox regression.

However, the importance of family relative to abuse history can be captured by a coefficient of variation (CV) defined by the ratio of the standard deviation of the random family effect to the absolute value of the estimate of the fixed effect of abuse history.

Ninety-five percent confidence intervals (CI's) are included in the tables whenever it was possible to compute them.

RESULTS

Clinical Description of Study Sample

All subjects were followed for 6.5 ± 3.5 years and were last evaluated at age 26.1 ± 8.2 years. Of the 548 subjects, physical abuse history status data were available on 533 and sexual abuse history on 535. Of the 533 with known childhood physical abuse status, the number with physical abuse history was 87 (16.3%). Of the 535 with known childhood sexual abuse status, the number with sexual abuse history was 59 (11.0%) (see Table 1). We had both physical and sexual abuse history on 532 subjects.

Thirty-five (6%) of the subjects had received a diagnosis of bipolar disorder. One hundred and ninety-seven (36%) had received a diagnosis of mood disorder. One hundred and sixty-six (30%) reported having used an antidepressant.

Relationship of Types of Childhood Abuse to Each Other and to Potential Mediators

Table S1 in the Supplementary Materials is a 2×2 table showing the relationship between the two types of abuse. The Chi^2 p-value for that table was 1.36×10^{-07}. The presence of one kind of abuse increased the chance that the other kind was also present.

The onset of mood disorder before age 16 years was more common in those with physical abuse before age 16 years compared with those without physical abuse ($p = 0.0024$; odds ratio = 2.23; 95% CI = 1.33–3.74). The onset of mood disorder before age 16 years was *not* significantly more common in those with sexual abuse compared with those without sexual abuse before age 16 years ($p = 0.54$; odds ratio = 1.23; 95% CI = 0.64–2.37).

Compared with males, females were 2.3 times more likely to report a history of sexual abuse (logistic regression: odds ratio = 2.58; 95% CI 1.45–4.58; $p = 0.001$) but no more likely to report a history of physical abuse (logistic regression: odds ratio = 1.09, 95% CI 0.69–1.72; $p = 0.72$). Female sex alone did not predict a suicide attempt ($p = .47$; hazard ratio (HR) = 1.30; 95% CI [0.64, 2.63]).

Relationship 1: Childhood Adversity Predicts Suicide Attempt

Table 2 shows results from the analysis testing relationship (1), *viz.*, CA as a predictor of a suicide attempt. Both sexual ($p = .001$; HR = 3.59; 95% CI [1.68, 7.67]) and physical abuse ($p = .024$; HR = 2.48; 95% CI [1.13, 5.46]) predicted future suicide attempt. The family effect coefficient of variation for sexual abuse predicting suicidal behavior was negligible, 1.6%. But for physical abuse, the CV was substantial, 79.2%.

TABLE 2. Results for Cox regression for childhood abuse history as a predictor of a suicide attempt (analysis type 1).

Abuse type	*n*	Hazard ratio (HR)	95% CI (HR)	*p*-Value
Sexual	535	3.59	1.68–7.67	0.001
Physical	533	2.48	1.13–5.46	0.024

TABLE 3A. Results for linear mixed models (analysis type 2) with history of abuse as the predictor and mean BGz as the dependent variable.

Variable	*n*	Coef. value[a]	95% CI[a]	*p*-Value
Sexual abuse	486	0.559	0.284–0.834	1×10^{-4}
Physical abuse	486	0.568	0.329–0.806	<0.0001

[a]Average BGz expressed in standard, i.e., standard deviation, units of mean BGz.

This suggests that sexual abuse history is a more powerful predictor of future suicide attempts than other familial factors. The reverse is true for physical abuse.

Relationship 2: Childhood Adversity Predicts Mediators

Table 3A displays the results of linear mixed model regressions testing relationship (2) for aggressive trait severity. The presence of either sexual ($p = 0.0001$) or physical abuse ($p < 0.0001$) was associated with an increase in BGz of about six-tenths of a standard deviation (95% CI (sexual abuse) [0.28, 0.83]; 95% CI (physical abuse) [0.33, 0.81]). Also, Figure 1 shows that childhood sexual and physical abuse were both associated with greater aggression.

Sex was associated with aggression trait severity ($p = 0.001$), being about a quarter standard deviation more severe in males (95% CI: [0.096, 0.372]). To study the impact of sex and abuse on aggression severity we fitted the model, $BGz = abuse + sex + abuse{:}sex$, where "abuse:sex" is the abuse-sex interaction. In females, the net effect of a history of childhood physical abuse increased BGz by 0.60 *SD*s ($p = 0.0003$; 95% CI = 0.28–0.93). In males, a history of childhood physical abuse increased BGz by 0.56 SDs ($p = 0.0006$; 95% CI = 0.24–0.8875060). In females, a history of childhood sexual abuse increased BGz by 0.39 SDs ($p = 0.02$; 95% CI = [0.06, 0.7]). In males, a history of childhood sexual abuse increased BGz by 1.12 SDs ($p = 4 \times 10^{-11}$; 95% CI = [0.67, 1.57]), about three times the effect seen in females.

Testing relationship (2) for a mood disorder, namely CA prediction of mood disorder onset, involved a Cox Regression Analysis as shown in Table 3B. Sexual abuse ($p = 0.001$, HR = 2.08, 95% CI [1.35, 3.20]) and physical abuse ($p = 0.023$, HR = 1.63, 95% CI [1.07, 2.48]) each predicted mood disorder onset. Figure 2 shows survival plots of the effect of sexual and physical abuse on mood onset, and both were associated with an elevated risk that persisted for over 15 years after the age of 16 years.

Relationship 3: Mediators Predict Suicide Attempt Adjusting for CA

First, we tested relationship (3) for aggression severity and mood disorder onset separately. To demonstrate a mediation effect requires the mediator to predict risk after

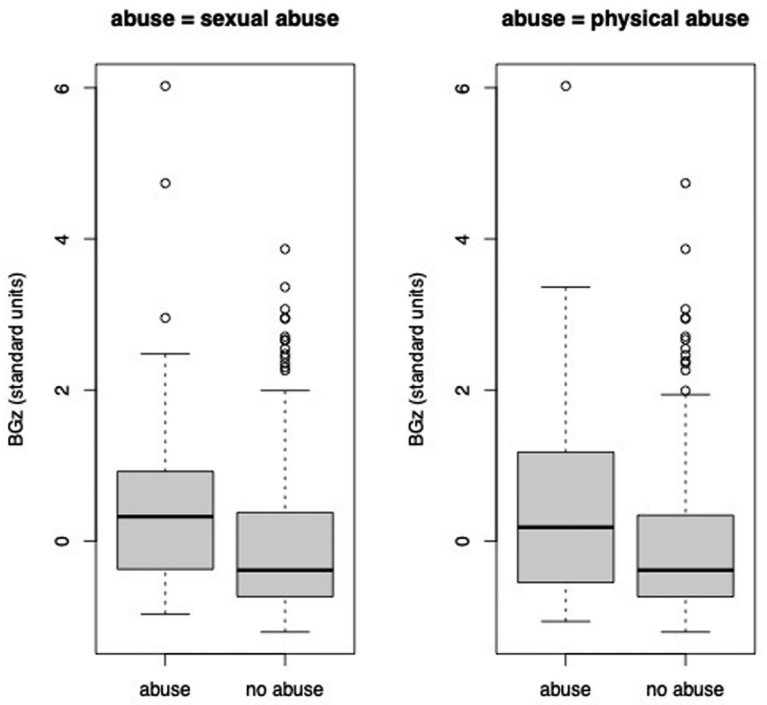

FIGURE 1. Aggression by abuse and abuse type. Standardized combined adult child z-scores (i.e., Mean = 0; SD = 1) by abuse type. Portrays a type (2) relationship.

TABLE 3B. Results for Cox regressions (relationship 2) with abuse as the predictor and onset of mood disorder as the dependent variable.

Abuse type	*n*	Hazard ratio (HR)	95% CI (HR)	*p*-Value
Physical	428	1.63	1.07–2.48	0.023
Sexual	430	2.08	1.35–3.20	.001

adjusting for CA, and a reduction or elimination of the risk predicted by CA, depending on whether the mediator explains part or all of the effect of CA on suicide attempts.

The results of the analysis for aggression are in Table 4A. Adjusting for sexual abuse, increasing BGz by one standard deviation corresponded to a hazard ratio of 1.77 ($p = 0.0007$, 95% CI [1.27, 2.47]). Adjusting for physical abuse, the hazard ratio was 1.95 ($p = 4.5 \times 10^{-5}$, 95% CI = [1.41, 2.69]). In this mediation analysis, neither the main effect of sexual abuse ($p = 0.11$, HR = 2.33 compared to 3.59 in relationship 1) nor physical abuse ($p = 0.93$, HR = 0.956 compared to 2.48 in relationship 1) was statistically significant, indicating that the mediator, aggression severity, accounts for some suicide attempt risk explained by sexual or physical abuse. Figure 3 portrays the relationship between childhood abuse history and aggression severity on one hand and suicide attempts on the other.

We estimated that childhood history of sexual abuse, indirectly through its effect on BGz or aggression severity, i.e., along the pathway *sexual abuse aggression attempt,* increased the hazard of a suicide attempt by 38% (95% bootstrap CI: 1–100%). By virtue of its effect on BGz, a history of physical abuse increased the hazard of the attempt by

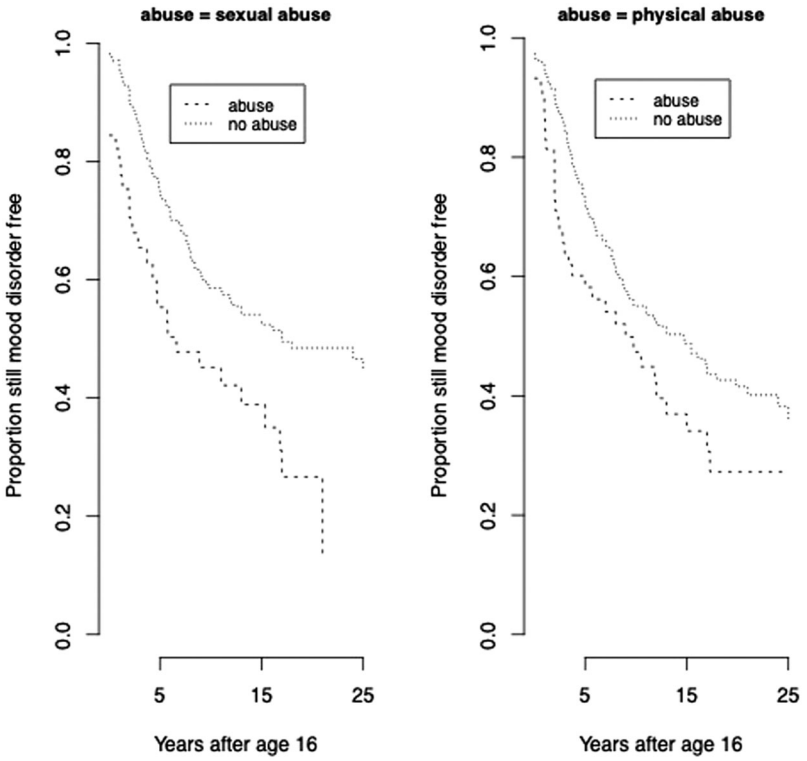

FIGURE 2. Mood onset survival curves by abuse and abuse type. Survival until mood disorder onset by abuse type. Portrays a type (2) relationship.

TABLE 4A. Relationship 3 Cox regressions with abuse and aggression as predictors of a suicide attempt.

Abuse type (coefficient name)	*n*	Hazard ratio (HR)[a]	95% CI (HR)[a]	*p*-Value
Sexual (abuse)	486	2.33	0.83–6.52	0.110
Sexual (BGz)	486	1.77	1.27–2.47	0.0007
Physical (abuse)	486	0.956	0.33–2.79	0.93
Physical (BGz)	486	1.95	1.41–2.69	4.5×10^{-5}

[a]For final average BGz hazard ratio and CI corresponds to increase by one *SD* (0.826).

46% (95% bootstrap CI: 3–125%). Because of the temporal nature of mood disorder onset, we were unable to measure the net effect of a history of abuse acting through its effect on the hazard of mood disorder onset.

BGz remains a mediator of abuse history even after adjusting for sex and its interaction with an abuse history. Here, the type 3 analysis is $attempt = BGz + abuse + sex + abuse{:}sex$. For example, for the model with physical abuse, the *p*-value of the main effect of mean BG was 0.0001, hazard ratio 1.86 (per *SD*), with 95% CI 1.35–2.56.) In the comparative analysis with sexual abuse in place of BGz, the *p*-value of mean BG was 0.001, and the hazard ratio was 1.76 (per *SD*), with 95% CI 1.09–2.42.

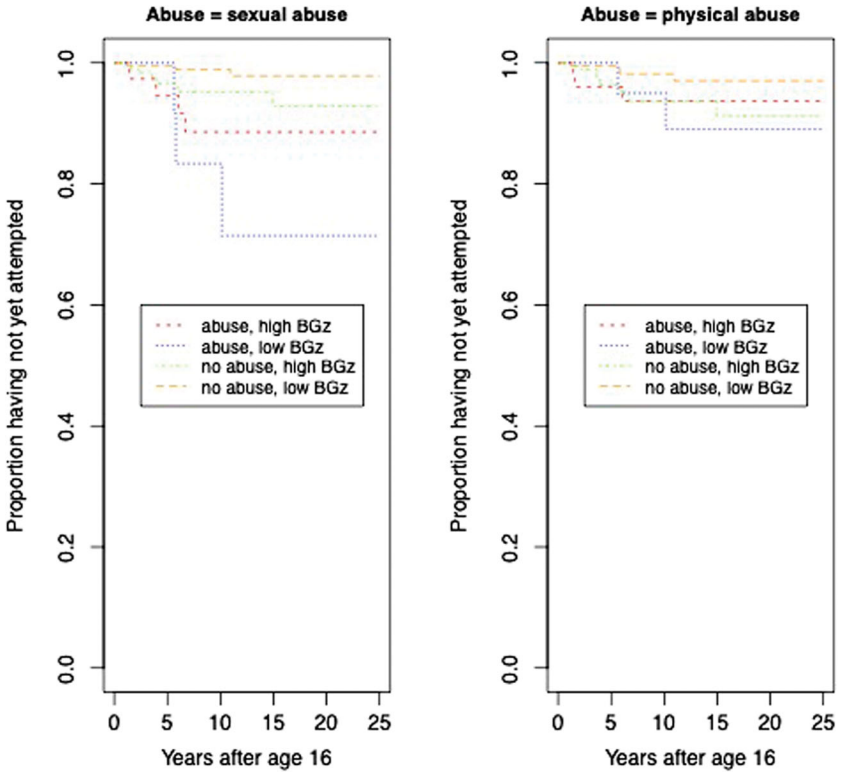

FIGURE 3. SA survival curves by abuse, aggression, and abuse type. Survival until SA, by abuse, dichotomized BGz (median split; median= -0.33 SD's), and abuse type. Portrays a type (3) relationship that includes the abuse-BGz interaction.

TABLE 4B. Relationship 3 Cox regressions with mood onset age and CA as possible predictors of suicide attempt.

Abuse type (coefficient name)	*n*	Hazard ratio (HR)	95% CI (HR)	*p*-Value
Physical (abuse)	429	1.23	0.39–3.90	.72
Physical (mood onset)	429	5.84	2.15–15.87	0.0005
Sexual (abuse)	431	1.86	0.63–5.48	.26
Sexual (mood onset)	431	5.28	1.91–14.56	0.0013

Another pathway, through which history of abuse affects suicide attempt hazard, is through its effect on mood disorder onset. Table 4B summarizes analyses testing relationship (3) for mood disorder onset as a mediator of the effect of CA on suicide attempts. Adjusting for sexual abuse, the onset of mood disorder was associated with suicide attempts with an HR of 5.28 ($p = 0.0013$, 95% CI [1.91, 14.56]). Adjusting for physical abuse, the HR was 5.84 ($p = 0.0005$, 95% CI [2.15, 15.87]). The main effect of sexual abuse ($p = 0.26$, HR = 1.86 compared to 3.59 in relationship 1) or physical abuse ($p = 0.72$, HR = 1.23 compared with 2.48 in relationship 1), were not statistically significant. A mediation effect of mood disorder onset is indicated because its inclusion eliminates the statistical significance of the relationship between CA and suicide attempts.

TABLE 5. Results for Cox regressions (analysis type 3) with first attempt as dependent variable and mood onset age and aggressivity and their interaction as possible compound mediator.

Abuse type	Change	Hazard ratio	*p*-Value	95% CI for hazard ratio
Physical	Abuse[a]	0.30	0.247	0.04–2.33
Physical	Mood (w/ avg BGz)[b]	3.99	0.047	1.02–15.59
Physical	Mood (w/ hi BGz)[c]	1.85	0.363	0.49–6.96
Physical	Mood (w/ lo BGz)[d]	8.59	0.022	1.37–54.03
Physical	BGz up (w/ mood)[e]	1.23	0.563	0.61–2.50
Physical	BGz up (no mood)[f]	2.66	0.000	1.64–4.30
Physical	Both BGz and mood included (*vs.* neither included) (LRT)[g]	NA	0.002	NA
Sexual	Abuse[a]	1.20	0.805	0.29–4.96
Sexual	Mood (w/ avg BGz)[b]	3.70	0.066	0.92–14.91
Sexual	Mood (w/ hi BGz)[c]	1.77	0.407	0.46–6.80
Sexual	Mood (w/ lo BGz)[d]	7.73	0.035	1.16–51.75
Sexual	BGz up (w/ mood)[e]	1.21	0.622	0.57–2.56
Sexual	BGz up (no mood)[f]	2.53	0.000	1.51–4.24
Sexual	Both BGz and mood included (*vs.* neither included) (LRT)[g]	NA	0.006	NA

Table shows *changes* in hazard with indicated changes in variables (interaction of BGz and mood onset in the model means the effect of BGz depends on whether mood disorder is already present or not and *vice versa*). *Offspring only* (394 subjects).

[a]History of abuse compared to absence, all else held equal.

[b]Effect of mood when BGz is at average value (i.e., final mean BGz $= -0.031$).

[c]Effect of mood when BGz is one *SD* (0.76) above average.

[d]Effect of mood when BGz is one *SD* below average.

[e]Effect of increase in BGz by one *SD* after onset of mood disorder (effect of decrease by one *SD* is just the reciprocal of this).

[f]Effect of increase in BGz by one *SD* before onset of mood disorder (effect of decrease by one SD is just the reciprocal of this).

[g]Likelihood Ratio Test, comparing model to one with only abuse, i.e., test of overall effect of mood and aggression.

The Combined Effect of Both Mediators on the Relationship of CA to Suicidal Behavior

To better understand the joint behavior of mood disorder onset and aggression, we first examined the relationship between aggression severity and mood disorder onset. In a mixed-effects Cox regression of mood onset with BGz as the predictor, an increase in BGz by one SD corresponded to an HR of 1.48 (95% CI [1.26, 1.73], $p = 1 \times 10^{-6}$). Since mood disorder is a state and aggression is a trait, and the trait precedes the onset of the state of mood disorder, it makes little sense to check if mood disorder onset predicts aggression.

We investigated whether aggression and mood disorder onset in combination acted as a mediator, by including aggression score, mood disorder onset, and their interaction as terms in relationship 3 Cox regressions (Table 5). We found that in this context, neither sexual ($p = 0.81$, HR $= 1.20$) nor physical ($p = 0.25$, HR $= 0.30$) abuse were significant as a predictor of a suicide attempt. Thus, if aggression, mood onset, and their interaction are in the model, adding abuse did not significantly affect suicide attempt hazard, thereby demonstrating that mood and aggression and their interaction term, mediate the effect of CA on suicide attempts.

However, if abuse history is in the model, adding aggression, mood disorder, and their interaction on suicide attempt risk did significantly modify attempt hazard (physical abuse: likelihood ratio test $p = 0.002$; sexual abuse: $p = 0.006$). It is not possible to assign a numerical value to the overall net effect of the mediators. Still, this set of findings is consistent with mood disorder onset and aggression severity mediating the relation between CA and suicide attempts.

When an interaction among two or more variables is included in a regression, it is difficult to interpret the individual coefficients pertaining to those variables. In Table 5, we describe the effects of several scenarios involving different levels of aggression and/or mood disorder onset. For example, adjusting for physical abuse history, the onset of mood disorder in the presence of an average level of aggression (as measured by BGz) still increased the hazard of suicide attempt by a factor of 4 ($p = 0.047$; 95% CI [1.02, 15.59]). But, with sexual abuse in place of physical abuse in the model, the effect of mood onset in the presence of an average level of aggression, was not quite significant ($p = 0.07$, HR = 3.70).

When aggression is high, the onset of mood disorder did not significantly further increase the suicide attempt hazard (physical abuse: $p = 0.36$ and HR = 1.85; sexual abuse: $p = 0.41$ and HR = 1.77). Conversely, the biggest effect of the onset of a mood disorder on suicide attempt hazard was the presence of low aggression (physical abuse: HR = 8.6 ($p = 0.02$; 95% CI [1.37, 54.0]); sexual abuse: HR = 7.7 ($p = 0.035$; 95% CI [1.16, 51.8]).

Adjusting for physical abuse, an increase in BGz by one standard deviation, before mood disorder onset, was associated with an HR for suicide attempt of 2.66 ($p = 0.000$, 95% CI [1.64, 4.30]). Adjusting for sexual abuse, an increase in BGz by one standard deviation, before mood disorder onset, was associated with an HR for suicide attempt of 2.53 ($p = 0.000$, 95% CI [1.51, 4.24]). However, once the mood disorder has begun, increasing BGz by 1 SD did not change the HR to a significant degree (physical abuse: $p = 0.56$ and HR = 1.23; sexual abuse: $p = 0.62$ and HR = 1.21). These examples indicate that adjusting for abuse, once either aggression or mood disorder is present, adding the other risk factor does not increase suicide attempt risk.

DISCUSSION

In agreement with previous studies from our group and others (Brodsky & Stanley, 2008; Brown & Anderson, 1991; Bryant & Range, 1997; Davidson, Hughes, George, & Blazer, 1996; Felitti et al., 2019; Gould et al., 1994; Harford et al., 2014; Kaplan, Asnis, Lipschitz, & Chorney, 1995; Lipschitz et al., 1999; Roberts & Hawton, 1980; Roy, 2002; Shaunesey, Cohen, Plummer, & Berman, 1993; Stepakoff, 1998; Van der Kolk, Perry, & Herman, 1991; Windle, Windle, Scheidt, & Miller, 1995), we found that reported childhood sexual or physical abuse predicted future suicidal behavior. We also found that CA predicted potential mediators, future mood disorder, and aggression severity, as previously reported (Björkenstam et al., 2017; Liu, 2017; Mall et al., 2018; Mumford et al., 2019). We found, as reported by our group and others (Brent et al., 2015; Brodsky & Stanley, 2008; Franklin et al., 2017; Miller et al., 2017), that these potential mediators predicted suicidal behavior.

After the age of 21 years in our study sample (that included only offspring of a parent with a mood disorder), 9.9 ± 6.0% of the variance of BGz was between families, 44.4 ± 6.2% was within families, and 45.7 ± 4.2% was *within* subjects, indicating that aggressivity, at least as measured by BG, does vary over time, but is strongly determined by the individual within families. We find that this effect over time was independent of age. Others report that mood disorders like bipolar disorder can be associated with anger attacks, irritability, and aggressive behaviors (Mesbah et al., 2021). Transitory fluctuations in aggression might be associated with attempts. However, in this paper, we

are interested in the trait of aggression determined by child abuse. To measure the trait-like component of aggression, the component that might be driven to some extent by CA, we averaged BGz across time points separately for each subject to minimize the impact of fluctuations in aggression.

What is new in the findings of the present study, is that we found that both mood disorder and aggression each mediated the relationship between reported childhood adversity and later suicide attempts. The effect of CA on suicide attempt risk was mediated by both mood disorder onset and aggression severity to a similar degree. Moreover, we found that when one of the mediators is present, the presence of the other did not significantly increase the hazard.

Only a minority of offspring in this study who made a suicide attempt also reported a history of childhood sexual or physical abuse. Therefore, other factors, such as genetic and other types of gene-environment interactions, must also contribute to the familial transmission of suicidal behavior.

In general, differences between males and females were consistent with the literature (Rudolph & Flynn, 2007; Wainwright & Surtees, 2002): females were more likely to report sexual abuse in childhood. Female sex increased the hazard of mood disorder onset (Hodes & Epperson, 2019) and both males and females become more aggressive as a result of childhood abuse (Cullerton-Sen et al., 2008). Of note, a history of sexual abuse had a bigger impact on male aggression. Aggression remained a mediator of the effect of CA on future suicide attempts even after adjusting for sex and its interaction with an abuse history. That finding is consistent with other studies that linked aggressive traits to childhood adversity in males alone and to suicidal behavior in males and females (Bridge et al., 2015; Fite et al., 2017; Gvion, 2018; Keilp et al., 2006; McCloskey & Ammerman, 2018).

The family effect coefficient of variation for sexual abuse was negligible, 1.6%. But for physical abuse, the coefficient of variance was substantial, 79.2%. This suggests that family variation does little to change the effect of a history of sexual abuse on future suicide attempts, while the effect of physical abuse history on future suicide attempts is subject to substantial between-family variation.

Most previous studies of mediational pathways between childhood adversity and suicidal behavior lacked a prospective design. However, longitudinal research examining mediational pathways between childhood adversity and self-harm (Russell et al., 2019) found adverse childhood experiences were associated with increased risk for self-harm. Given that we found both mood disorder and aggression, separately and interactively, mediated the relationship between childhood adversity and suicide attempt, this is a new observation, as are the observed complex interactions between sex and type of CA in terms of impact on mediators. The interaction of these mediators has not been fully appreciated to date. Not only do mood disorders and aggressive traits each mediate the effects of CA on the risk of suicidal behavior later in life, but more pronounced aggressive traits are associated with an earlier onset mood disorder, as we previously reported in a different study sample (Mann et al., 2005). Males have more robust aggressive traits compared with females as we report previously in a different study sample (Oquendo et al., 2007), and this has implications for rates of earlier onset mood disorders and for mediation effects on suicidal behavior. Broadly speaking, sexual abuse in childhood, reported more commonly in women, has a more robust association with future suicidal behavior than does physical

abuse, and that effect is more strongly mediated via mood disorder than by aggressive trait severity. Others report that type of childhood abuse can mean different risks for future mood disorders (Infurna et al., 2016) or future aggressive traits (Mumford et al., 2019). More longitudinal work on the time course and interaction effects of these factors in mediational pathways is needed to replicate and extend these findings.

Epigenetics may moderate the relationship between childhood adversity and psychopathology. This could occur through DNA methylation, as it has been hypothesized that early life stress impacts DNA methylation and other epigenetic mechanisms (Petronis, 2010). However, recent research does not support the hypothesized effect of childhood adversity on DNA methylation after accounting for confounding variables, e.g., family background (Marzi et al., 2018). Therefore, more research is needed to determine how epigenetics may contribute to the disruption of HPA axis responses, inflammatory processes, and neurotransmitter systems and thereby moderate the risk of suicide (Haghighi et al., 2014).

Another pathway involves gene-environment interactions and examples can be seen in some functional polymorphisms in genes, such as the serotonin transporter promotor variants (*HTTLPR*), glucocorticoid receptor (*GR*), and monoamine oxidase A (*MAOA*) (Fanning, Lee, Gozal, Coussons-Read, & Coccaro, 2015; Provençal et al., 2015; Reif et al., 2007; Weeland, Overbeek, de Castro, & Matthys, 2015) that are associated with mood disorders and aggression more strikingly in those with reported CA. Serotonin hypofunction contributes to both the pathophysiology of mood disorders, aggressive and suicidal behaviors (Bortolato et al., 2013; Coryell et al., 2018; Glick, 2015). The interaction between childhood adversity and low activity MAOA genotype may mediate the formation of antisocial behavior (Byrd & Manuck, 2014). Other genes are hypothesized to be also involved, such as genes encoding for inflammation, namely IL-6 and TNFalpha (Miller & Cole, 2012).

Limitations of this study are that we had to exclude half of the suicide attempters because their suicide attempts occurred before age 16 years and we did not have a more detailed temporal breakdown of when childhood adversity took place other than that it was before age 16 years. Perhaps such a more detailed temporal breakdown of when the abuse took place may not help in the event that the abuse must be some combination of being prolonged and sufficiently severe to have these adverse consequences. We did observe that the occurrence of one type of abuse, increased the likelihood of the other type of abuse. Baseline aggression and mood disorder information, as with most psychiatric studies, was retrospective and therefore subject to recall bias, perhaps mitigated because this was a study in younger individuals. History of child abuse, as measured by one or more of the CEQ, CARE, CTQ, and BDEMO, was captured in a binary variable of "± abuse before 16 years" rather than along a continuum of severity. As such, applying the severity of childhood adversity to these analyses must await a future study. We use survival methods to study suicide attempts and the onset of mood disorders in the presence of censoring. These methods are based on the assumption that the mechanisms which led to the events in question, and to dropout, operate independently of one another. That assumption is difficult to check. Additionally, we could not account for some other possible confounders, including treatment effects, social determinants of health, genetic liability, and severity or duration of childhood adversity. We did not examine the impact of childhood abuse on the lethality of suicidal behavior or the impact of childhood deprivation experiences because these are complex next steps requiring more granular data sets involving a larger subgroup manifesting suicidal behavior than in this study.

This study has important clinical implications. Specifically, results support prevention approaches that emphasize the treatment of depression and the amelioration of aggressive behaviors in children and adults with childhood abuse history to reduce future suicide risk. Future work should include a closer inspection of the relationship between aggression and mood disorder onset and determine whether self- or clinician-assessed severity of childhood adversity is better associated with suicidal behavior as an adult. Moreover, the biological underpinnings of mood disorder and aggression may help clarify genetic and epigenetic effects resulting in suicide attempt behavior. Our prospective approach to the causal pathways of childhood adversity to suicidal behavior indicates important modifiable potential suicide prevention targets that should be the subject of future research on the amelioration of suicide risk.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available to NIH funded investigators upon request directed to the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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