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# Gene-environment interaction between HPA-axis genes and trauma exposure in the suicide behavior: A systematic review

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ABSTRACT

Suicide behavior (SB) emerge from complex interactions among traumatic events and multiple genetic factors. We conducted the first systematic review to assess the evidence of a link among trauma exposure, HPA-axis genes, and SB. A systematic search of PubMed, EBSCO, Science Direct, PsychInfo, and Scopus databases on gene-environment interaction, and susceptibility to SB was carried out until February 2022. Our study was prospectively registered in PROSPERO (CRD42022316141). A total of 13 epidemiological studies (11,756 subjects) were included: eight studies focused on traumatic experiences in the childhood and five studies on lifetime trauma exposure. All studies reported a positive association between the trauma exposure with SB. Gene-environment interaction was reported for *CRHR1* (n = 6), *CRHR2* (n = 2), *FKBP5* (n = 2), and *CRHBP* (n = 1), however, for *CRH, NR3C1, MC2R,* and *POMC* genes no found gene-environment effects on SB. Trauma exposure could be one mechanism that links HPA-axis genes activity with the development of SB.

## 1. Background

Exposure to traumatic events is associated with emotional and behavioral problems that are common experience of childhood and that persist in the adulthood. Emotional and behavioral symptoms could be interpreted as indicators of individuals vulnerability that are often correlated with socioeconomic strain, familial instability, or family dysfunction (Bremner and Wittbrodt, 2020; Copeland et al., 2007).

Several studies have found that childhood trauma exposure increases the risk of suicidal ideation (SI) and suicide attempts (SA). Moreover, lifetime trauma exposure also is strongly associated with suicide behavior (SB) risk in military personnel (Angelakis et al., 2019; Copeland et al., 2018; Ryan et al., 2020). Trauma can has lasting effects on neurotransmitter and neurohormonal systems involved in the stress response. The hypothalamic-pituitary-adrenal (HPA) axis is activated by stress and involves the interaction of numerous chaperones, hormones, and receptors (De Luca et al., 2010).

In response to acute stress, hypothalamic corticotropin releasing hormone (CRH) stimulates the release of adrenocorticotropic hormone (ACTH) derives from the cleavage of the precursor hormone pro-opiomelanocortin (POMC); which in turn stimulates the release of the hormone cortisol via the melanocortin receptor (MC2R) (Herman et al., 2016; Jenks, 2009). Cortisol binding to the glucocorticoid receptor (GR) and the translocation of the GR from the cytoplasm into the nucleus is moderated by FK506 binding protein 51 (FKBP51) (Binder, 2009; Roy et al., 2012). The availability of CRH is regulated by a high-affinity binding protein (CRHBP) and a large proportion of CRH is complexed with CRHBP and therefore, unavailable for CRHR1 and CRHR2

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receptors activation (Westphal and Seasholtz, 2006).

Genetic variation in any of these HPA-axis regulators genes may interfere with the functioning of this pathway, moreover, several single nucleotide polymorphisms (SNP's) have been associated with the SB (Hernández-Díaz et al., 2021a, 2021b). Stress-diathesis model states that SB is the result of an interaction between acutely stressful events; such as trauma, and a susceptibility to SB (a diathesis) [9].

To the best of our knowledge, this study was the first to analyze gene-environment interaction (G x E) in suicide. The aim of this study was to investigate whether genetic variation in HPA-axis genes interacts with a childhood trauma and/or lifetime trauma to increase the risk of suicidal behavior. We selected genes that have been analyzed in at least two studies. Due to above, this systematic review included eight genes: *FKBP5, CRH, CRHR1, CRHR2, CRHBP, NR3C1, MC2R,* and *POMC*.

## 2. Materials and methods

We conducted this systematic review of studies investigating the relationship between trauma exposure and HPA-axis genes in the SB, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study was registered in International Prospective Register of Systematic Reviews (PROSPERO, CRD42022316141).

### 2.1. Literature search

To identify all primary research findings, we consulted five databases before 25 February 2022: PubMed, EBSCO, Science Direct, PsychInfo, and Scopus. The search strategy applied the following combination of terms: ((child maltreatment) OR (traumatic event) OR (trauma exposure)) AND (HPA-axis gene) AND ((suicide) OR (suicide behavior)). Reference lists of potentially eligible articles were also screened.

### 2.2. Selection criteria

Suicide behavior was defined as self-harming behaviors undertaken with an intention of ending one's own life. SB exists on a spectrum of severity that include the suicide ideation (thinking or planning to commit suicide), and the suicide attempt (potentially self-injurious behavior associated with at least some intent to die) (Serrano and Dolci, 2021).

The following inclusion criteria must have been satisfied: (1) epidemiological observational studies; (2) evaluating the interaction of a trauma exposure; (3) with HPA-axis genes (SNP's); (4) in patients with SB. Studies were excluded if they: (1) were not written in English; (2) they were conducted in animals; and (3) they had the structure of unpublished reports, abstracts, reviews, meta-analyses, and letters.

### 2.3. Data extraction and quality assessment

All possible articles were independently reviewed by two investigators (Y.H.D & T.B.G.C), followed by data extraction. Any discrepancies were resolved by discussion with another investigator (C.A.T.Z). The following information was extracted by two investigators: first author, study year, sample size, type of SB, nature of adversity, instruments, adversity measurement, gene, SNP's, and main findings.

### 2.4. Assessment of quality and risk of bias

For the quality assessment of included studies in the systematic review, the Newcastle-Ottawa Scale (NOS Scale) was employed to ascertain the quality of studies by two reviewers (Y.H.D & T.B.G.C). It consisted of 3 parts which were the selection, comparability, and outcomes. We gave points if the studies met related condition. Studies with scores of 0–3, 4–6, 7–9 were, respectively, considered as low, moderate, and high quality.

Risk of bias for non-randomized studies was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) Assessment Tool. ROBINS-I scale evaluates the risk of bias in "low risk", "moderate risk", "high risk", and "critical risk"; in the domains "selection", "intervention", "missing data", "confusion", "measurement of results", "report", and an overall evaluation expressed in "global risk of bias".

### 2.5. Data analysis

A qualitative synthesis of all the included studies was performed based on the outcome of interest, and the findings were reported in tabular form for easy interpretation. Due to the expected diverse nature of the identified studies and their outcomes, this systematic review will not attempt any meta-analyses.

## 3. Results

Our search generated 317 records, with 220 remaining after filtering out duplicates (Fig. 1). Titles and abstracts were then screened, and of these, 139 were excluded and 81 studies were retained, and their full-text articles were assessed for eligibility. After applying the inclusion and exclusion criteria, 70 publications were removed. Finally, a total of 13 original studies on trauma exposure and HPA-axis genes were included in the systematic review (Ben-Efraim et al., 2011; Berent et al., 2020; Boscarino et al., 2022; Breen et al., 2015; Guillaume et al., 2013; Ludwig et al., 2018; Roy et al., 2010, 2012; Sanabrais-Jiménez et al., 2019; Segura et al., 2019; Wasserman et al., 2008, 2009; Zhang et al., 2019). Fig. 1 illustrates the selection process of this systematic review.

### 3.1. Quality assessment and risk of bias

The detailed results of the quality assessment based on the total score for the NOS scale for categories of selection, comparability and exposure/outcome are presented in Table 1. Overall the quality of the studies was moderate/high (range 6–9). Risk of bias of the included studies also is summarized in Table 1. The majority of studies had a low global risk of bias (8 studies).

### 3.2. Study characteristics

Thirteen articles reported about of candidate-gene or SNP-based studies and explored G × E interactions on SB risk, covering two environmental exposures (childhood trauma and/or lifetime trauma) and eight genes (*FKBP5, CRH, CRHR1, CRHR2, CRHBP, NR3C1, MC2R* and *POMC*) (Ben-Efraim et al., 2011; Berent et al., 2020; Boscarino et al., 2022; Breen et al., 2015; Guillaume et al., 2013; Ludwig et al., 2018; Roy et al., 2010, 2012; Sanabrais-Jiménez et al., 2019; Segura et al., 2019; Wasserman et al., 2008, 2009; Zhang et al., 2019).

Sample size ranged from 70 to 672 subjects with SB and 127 to 3623 controls, for a total of 11,756 subjects. All studies were published between 2008 and 2022, their mean age ranged from 24 to 43.4 years old. Structured Clinical Interview (SCID-I) for Diagnostic and Statistical Manual of Mental Disorders (DSM) was used as the primary diagnostic tool, however, other publications assessed the SB during the clinical interview using the Columbia Suicide Severity Rating Scale (C-SSRS), Clinical International Diagnostic Interview (CIDI) or International Classification of Diseases (ICD), which assesses current and lifetime suicidal ideation and attempts, intensity of ideation, and medical lethality of the suicide attempt.

Regarding the HPA-axis genes, 9 studies utilized blood, 1 saliva, and 1 buccal cells for genotyping. Details of the included studies are shown in Tables 2 and 3.

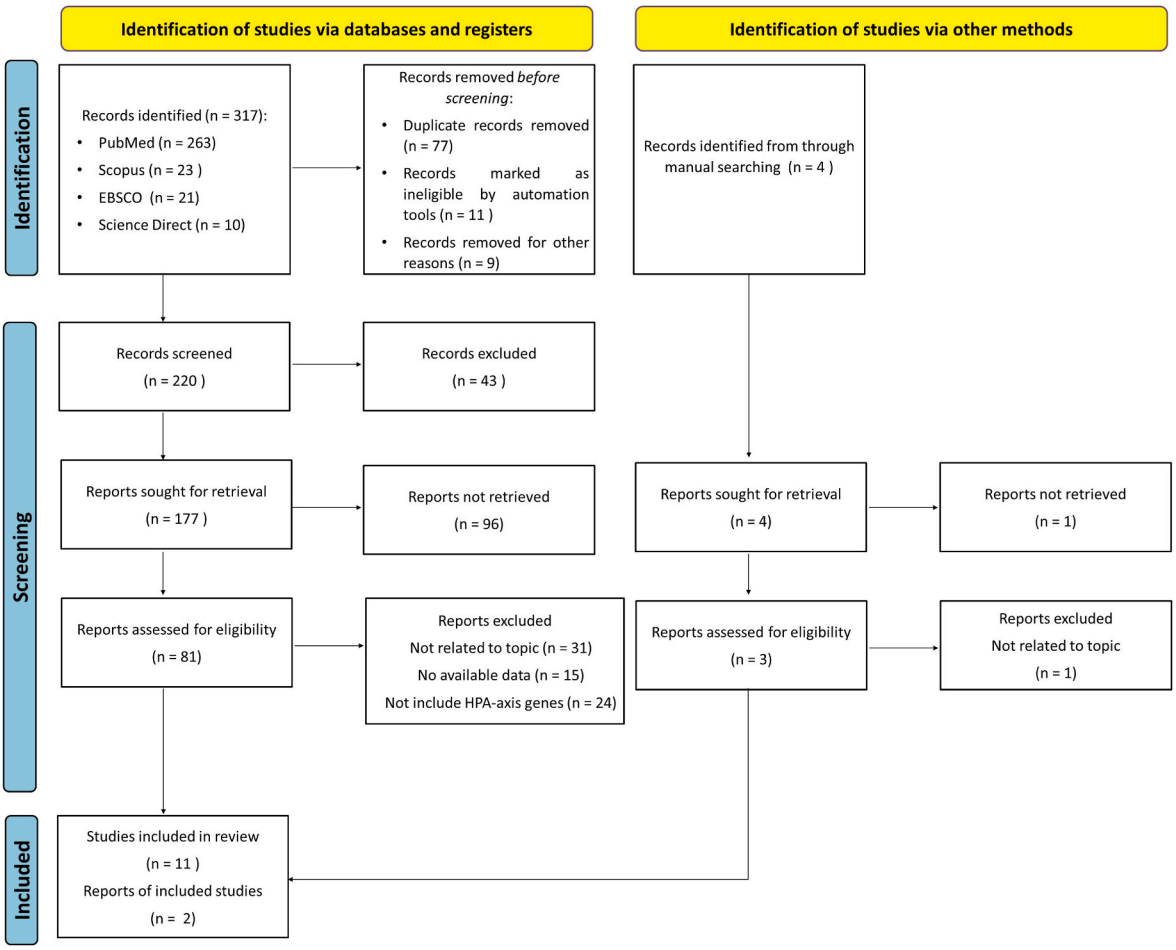


**Fig. 1.** Flow-chart of study selection for inclusion in the review.

**Table 1**
Quality assessment of studies included through the NOS scale and details bias risk assessment using the ROBINS-I tool.

| Study | NOS scale | | | | ROBINS-I tool | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Selection | Comparability | Outcomes | Total score | Selection | Intervention | Missing data | Confusion | Measurement of results | Report | Global risk |
| (Wasserman et al., 2008) | 2 | 2 | 3 | 7/9 | Moderate | Low | Moderate | Moderate | Low | Low | Moderate |
| (Wasserman et al., 2009) | 2 | 2 | 3 | 7/9 | Moderate | Low | Moderate | Moderate | Low | Low | Moderate |
| (Roy et al., 2010) | 4 | 2 | 2 | 8/9 | Low | Low | Low | Moderate | Low | Moderate | Low |
| (Ben-Efraim et al., 2011) | 3 | 2 | 2 | 7/9 | Low | Moderate | Low | Low | Low | Moderate | Low |
| (Roy et al., 2012) | 3 | 2 | 2 | 7/9 | Low | Low | Moderate | Low | Moderate | Low | Low |
| (Guillaume et al., 2013) | 2 | 2 | 2 | 6/9 | Moderate | Moderate | Low | High | Low | Low | Moderate |
| (Breen et al., 2015) | 4 | 2 | 2 | 8/9 | Low | Low | Low | Moderate | Low | Low | Low |
| (Ludwig et al., 2018) | 2 | 2 | 3 | 7/9 | Low | Moderate | Moderate | Low | Low | Low | Low |
| (Sanabrais-Jiménez et al., 2019) | 2 | 2 | 2 | 6/9 | Low | High | Moderate | Low | Low | Moderate | Moderate |
| (Segura et al., 2019) | 2 | 2 | 2 | 6/9 | Low | Low | Moderate | High | Low | Moderate | Moderate |
| (Zhang et al., 2019) | 3 | 2 | 2 | 7/9 | Moderate | Moderate | Low | Low | Low | Low | Low |
| (Berent et al., 2020) | 4 | 2 | 3 | 9/9 | Low | Low | Low | Moderate | Moderate | Low | Low |
| (Boscarino et al., 2022) | 3 | 2 | 3 | 8/9 | Low | Low | Moderate | Low | Low | Moderate | Low |

### 3.3. Trauma predictor instruments

First, traumatic experiences in the childhood were evaluated using the Childhood Trauma Questionnaire (CTQ) (Hernandez et al., 2013; Scher et al., 2001), Adverse Childhood Experience Questionnaire (ACE) (Felitti et al., 1998), or Early Life Events Scale (ELES) (Breen et al., 2015).

CTQ questionnaire asks the individuals to rate frequency of

**Table 2**
Descriptive summary of studies investigating suicide behavior associated with the trauma exposure.

| Study | SB | Cases | | | | Nature of adversity | Instrument | Adversity measurement | Adversity-related findings |
|---|---|---|---|---|---|---|---|---|---|
| | | N | Country (Ethnicity) | Male | Mean age | | | | |
| (Wasserman et al., 2008) | SA | 542 | Ukraine (Caucasian) | 276 | 24 | Stressful life events | SLEI | Number of stressful traumatic life events | SA was associated with stressful life events |
| (Wasserman et al., 2009) | SA | 672 | Ukraine (Caucasian) | 349 | 24.1 | Stressful life events | SLEI | Number of stressful traumatic life events | SA was associated with stressful life events |
| (Roy et al., 2010) | SA | 248 | USA (African–American) | 223 | – | Childhood maltreatment | CTQ | Physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse | SA was associated with higher childhood trauma scores |
| (Ben-Efraim et al., 2011) | SA | 660 | Ukraine (Caucasian) | 337 | 24.2 | Stressful life events | SLEI | Number of stressful traumatic life events | SA was associated with stressful life events |
| (Roy et al., 2012) | SA | 248 | USA (African–American) | 223 | – | Childhood maltreatment | CTQ | Physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse | SA was associated with higher childhood trauma scores |
| (Guillaume et al., 2013) | SA | 218 | France (Caucasian) | 64 | 39.71 | Childhood maltreatment | CTQ | Physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse | SA was associated with sexual abuse |
| (Breen et al., 2015) | SA | 631 | USA (Caucasian) | – | – | Childhood abuse | ELES | Physical and/or sexual abuse | SA was associated with a history of early childhood abuse |
| (Ludwig et al., 2018) | SA | 70 | Austria (Caucasian) | – | – | Childhood maltreatment | CTQ | Physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse | SA was associated with sexual abuse |
| (Sanabrais-Jiménez et al., 2019) | SA | 183 | Mexico (Latinoamerican) | 30 | 35.72 | Childhood maltreatment | CTQ | Physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse | SA was associated with childhood trauma |
| (Segura et al., 2019) | Mixed | 129 | Spain (Caucasian) | – | – | Childhood maltreatment | CTQ | Physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse | SB was associated with higher childhood trauma scores |
| (Zhang et al., 2019) | SI | 266 | USA (Caucasian) | 219 | 29 | Lifetime traumatic events | LEC | Number of life-time stressful events | SI was associated with stressful life events |
| (Berent et al., 2020) | SA | 176 | Poland (Caucasian) | 134 | 43.4 | Childhood adversities | ACE | Physical, verbal, and sexual abuse; emotional and physical neglect; several household dysfunctions; witnessing a family member's suicide attempt or death and witnessing stranger's death | SA was associated with a history of childhood maltreatment |
| (Boscarino et al., 2022) | Mixed | 597 | USA (Caucasian) | – | – | Lifetime traumatic events | TES | Number of life-time stressful events | SB was associated with stressful life events |

SA: Suicide Attempt; SI: Suicide Ideation; ACE: Adverse Childhood Experience; CTQ: Childhood Trauma Questionnaire; ELES: Questionnaire or Early Life Events Scale; LEC: Life Events Checklist; SLEI: Stressful Life Event Inventory; TES: Traumatic Event Scale.

traumatic events in the childhood using a one-to-five-point Likert scale. The CTQ yields scores for five traumas experienced in the childhood: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse, as well as a total score. For statistical analyses, publications reported the scores of each of the five subscales and/or the total CTQ score was used.

ACE questionnaire evaluate eight different experiences: physical, sexual, and emotional abuse, neglect, parental death, incarceration, alcoholism, and family suicidality. Publications reported an accumulative score created by summing the eight types of adverse experiences.

ELES instrument measure emotional memories, linked to recall of feeling devalued, frightened, and having to behave in a subordinate way. A history of physical and/or sexual abuse was analyzed using the ELES and the rates of early childhood abuse based on these questions were reported.

Second, lifetime trauma exposure was evaluated using the Stressful Life Event Inventory (SLEI) (Kendler et al., 2005), Life Events Checklist (LEC) (Zhang et al., 2019), or Traumatic Event Scale (TES) (Kilpatrick et al., 2003).

SLEI measure the amount of stressful traumatic life events among research subjects, across their life span. The questions covered experiences as: 'assault', 'divorce/separation', 'major financial problems', 'serious illness or injury', 'legal problems', 'loss of confidant', 'serious marital problems', 'robbed', 'serious difficulties at work', 'serious housing problems', and 'job loss'. All items were scored and grouped.

LEC is a commonly used self-report measure assessing experiences that meet the DSM-IV PTSD definition of a traumatic stressor. The number of lifetime stressful events was the total number of 'happened to me' events. Finally, TES also assessed the occurrence of lifetime traumatic events (e.g., forced sexual contact, domestic abuse, a serious accident, served in a warzone, experienced a disaster, etc.), and classifies into three categories: less than 3 traumatic events, 3–5 events, and 6 or more events, this ultimate was used for the authors to define "high" lifetime traumatic event exposure.

### 3.4. Association between traumatic experiences in the childhood and SB

We identified 8 studies (Berent et al., 2020; Breen et al., 2015;

**Table 3**
Descriptive summary of studies investigating G × E interaction.

| Study | Nature of adversity | N | | SB | Tissue | Gene | SNP | Risk allele | G × E interaction |
|---|---|---|---|---|---|---|---|---|---|
| | | Cases | Control | | | | | | |
| (Wasserman et al., 2008) | Stressful life events | 542 | – | SA | Blood | *CRH* | rs1870393 | C | Negative |
| | | | | | | | rs3176921 | G | |
| | | | | | | *CRHR1* | rs1396862 | A | Positive for rs4792887 |
| | | | | | | | rs4792887 | T | |
| (Wasserman et al., 2009) | Stressful life events | 672 | – | SA | Blood | *CRHR1* | rs4792887 | T | Positive for rs4792887, rs110402, and rs242939 |
| | | | | | | | rs110402 | A | |
| | | | | | | | rs12936511 | T | |
| | | | | | | | rs242939 | G | |
| | | | | | | | rs242938 | G | |
| | | | | | | | rs1876831 | T | |
| | | | | | | | rs16940665 | C | |
| (Roy et al., 2010) | Childhood maltreatment | 248 | 1217 | SA | Blood | *FKBP5* | rs3800373 | A | Positive |
| | | | | | | | rs9296158 | C | |
| | | | | | | | rs1360780 | C | |
| (Ben-Efraim et al., 2011) | Stressful life events | 660 | 284 | SA | Blood | *CRHR1* | rs7209436 | T | Positive for rs7209436, rs4792887, and rs16940665 |
| | | | | | | | rs4792887 | T | |
| | | | | | | | rs110402 | A | |
| | | | | | | | rs16940665 | C | |
| (Roy et al., 2012) | Childhood maltreatment | 248 | 1217 | SA | Blood | *FKBP5* | rs3800373 | A | Positive |
| | | | | | | *CRH* | rs6996265 | A | Negative |
| | | | | | | | rs3176921 | G | |
| | | | | | | | rs6472257 | T | |
| | | | | | | | rs5030875 | C | |
| | | | | | | *CRHR2* | rs3779250 | T | Negative |
| | | | | | | | rs973002 | A | |
| | | | | | | | rs8192498 | T | |
| | | | | | | | rs2190242 | A | |
| | | | | | | | rs2284217 | G | |
| | | | | | | | rs2014663 | T | |
| | | | | | | | rs6967702 | C | |
| | | | | | | | rs4723002 | G | |
| | | | | | | | rs255102 | T | |
| | | | | | | | rs255105 | C | |
| | | | | | | | rs255125 | C | |
| (Guillaume et al., 2013) | Childhood maltreatment | 218 | – | SA | Blood | *CRHR1* | rs242948 | T | Positive for rs242948, rs1396862, and rs878886 |
| | | | | | | | rs1396862 | A | |
| | | | | | | | rs878886 | T | |
| | | | | | | | rs4076452 | C | |
| | | | | | | *CRHR2* | rs2267716 | C | Negative |
| | | | | | | | rs11980048 | T | |
| | | | | | | | rs4723002 | G | |
| | | | | | | | rs2190242 | A | |
| | | | | | | | rs4723003 | T | |
| (Breen et al., 2015) | Childhood abuse | 631 | 284 | SA | – | *FKBP5* | rs6926133 | C | Negative |
| | | | | | | | rs12200498 | A | |
| | | | | | | | rs9380526 | T | |
| | | | | | | | rs16879378 | C | |
| | | | | | | | rs4713899 | G | |
| | | | | | | *CRH* | rs6990486 | A | Negative |
| | | | | | | | rs6472257 | T | |
| | | | | | | | rs7835214 | C | |
| | | | | | | | rs10957368 | C | |
| | | | | | | | rs10105164 | T | |
| | | | | | | *CRHR2* | rs4722999 | T | Negative |
| | | | | | | | rs2284219 | G | |
| | | | | | | | rs255115 | A | |
| | | | | | | | rs255102 | T | |
| | | | | | | *CRHBP* | rs7721799 | A | Negative |
| | | | | | | | rs2174444 | T | |
| | | | | | | | rs10473984 | T | |
| | | | | | | *MC2R* | rs3744819 | C | Negative |
| | | | | | | | rs12456733 | A | |
| | | | | | | | rs1941088 | A | |
| | | | | | | | rs3888305 | C | |
| | | | | | | | rs4308014 | T | |
| | | | | | | *NR3C1* | rs4912905 | C | Negative |
| | | | | | | | rs10042042 | A | |
| | | | | | | | rs17209251 | G | |
| | | | | | | | rs17100236 | C | |
| | | | | | | | rs10477211 | A | |
| | | | | | | *POMC* | rs7565877 | G | Negative |
| | | | | | | | rs6545975 | A | |
| | | | | | | | rs7565427 | C | |

(*continued on next page*)

**Table 3** (*continued*)

| Study | Nature of adversity | N | | SB | Tissue | Gene | SNP | Risk allele | G × E interaction |
|---|---|---|---|---|---|---|---|---|---|
| | | Cases | Control | | | | | | |
| | | | | | | | rs934778 | G | |
| | | | | | | | rs1866146 | A | |
| (Ludwig et al., 2018) | Childhood maltreatment | 70 | 181 | SA | Blood | *CRHR1* | rs7209436 | T | Positive for rs7209436 and rs110402 |
| | | | | | | | rs4792887 | T | |
| | | | | | | | rs110402 | A | |
| | | | | | | | rs242924 | T | |
| | | | | | | | rs242939 | G | |
| (Sanabrais-Jiménez et al., 2019) | Childhood maltreatment | 183 | 183 | SA | Blood | *CRHR1* | rs110402 | A | Positive |
| | | | | | | | rs242924 | T | |
| | | | | | | | rs16940665 | C | |
| | | | | | | *CRHR2* | rs2190242 | A | Positive |
| | | | | | | | rs2284217 | G | |
| | | | | | | | rs2014663 | T | |
| (Segura et al., 2019) | Childhood maltreatment | 129 | – | Mixed | Blood | *FKBP5* | rs3777747 | G | Negative |
| | | | | | | | rs1360780 | C | |
| | | | | | | | rs17542466 | C | |
| | | | | | | | rs2766533 | A | |
| | | | | | | *CRHR2* | rs4722999 | T | Negative |
| | | | | | | | rs2284219 | G | |
| | | | | | | | rs255115 | A | |
| | | | | | | | rs255102 | T | |
| | | | | | | *CRHBP* | rs7728378 | C | Negative |
| | | | | | | | rs10474485 | A | |
| | | | | | | *MC2R* | rs4797825 | T | Negative |
| | | | | | | | rs9961110 | C | |
| | | | | | | | rs17624314 | G | |
| | | | | | | *NR3C1* | rs6198 | C | Negative |
| | | | | | | | rs2963156 | C | |
| | | | | | | | rs1837262 | A | |
| | | | | | | | rs4912910 | G | |
| | | | | | | | rs4634384 | T | |
| | | | | | | *POMC* | rs713586 | C | Negative |
| | | | | | | | rs6713532 | C | |
| | | | | | | | rs6545975 | A | |
| | | | | | | | rs934778 | G | |
| (Zhang et al., 2019) | Lifetime traumatic events | 266 | 3623 | SI | Saliva | *FKBP5* | rs9470080 | C | Negative |
| | | | | | | | rs3800373 | A | |
| | | | | | | | rs9296158 | C | |
| | | | | | | | s1360780 | C | |
| (Berent et al., 2020) | Childhood adversities | 176 | 127 | SA | Buccal | *FKBP5* | rs1360780 | C | Negative |
| (Boscarino et al., 2022) | Lifetime traumatic events | 597 | – | Mixed | – | *FKBP5* | rs9470080 | C | Negative |
| | | | | | | *CRHR1* | rs110402 | A | Negative |

SA: Suicide Attempt; SI: Suicide Ideation.

Guillaume et al., 2013; Ludwig et al., 2018; Roy et al., 2010, 2012; Sanabrais-Jiménez et al., 2019; Segura et al., 2019) reporting on the association between traumatic experiences in childhood and HPA-axis genes. Several studies (n = 5) used a cross-sectional design based on retrospective measures with an exposed and a control group (Berent et al., 2020; Breen et al., 2015; Ludwig et al., 2018; Roy et al., 2010, 2012; Sanabrais-Jiménez et al., 2019). Notably, most studies were performed on a population with comorbidities, including patients with anxiety disorder, post-traumatic stress disorder, major depression disorder, and alcohol and drug use.

Traumatic experiences in the childhood included physical abuse, physical neglect, emotional abuse, emotional neglect, sexual abuse, parental death, incarceration, and alcoholism. All studies reported a positive association between the traumatic experiences in the childhood and the suicide behavior (Table 2). The most reported trauma subtype was emotional neglect, followed by emotional abuse, sexual abuse, physical neglect, and physical abuse.

Specifically, Breen et al., 2005 (Breen et al., 2015) found a significant association between a history of early childhood abuse and attempted suicide, while that, Guillaume et al., (2013) (Guillaume et al., 2013) and Sanabrais-Jiménez et al., (2019) (Sanabrais-Jiménez et al., 2019) reported an association between childhood sexual abuse and SA.

Considering quantitative scores in total and each subscale of CTQ, Segura et al. (2019) indicated that individuals with SB show higher scores of total CTQ score, emotional abuse, sexual abuse, and emotional neglect. Moreover, individuals with SA had higher CTQ scores irrespective of whether they were substance dependent (Roy et al., 2010, 2012). Ludwig et al., (2018) found a tendency of higher scores for females in comparison to males in all subscales, reaching statistical significance for sexual abuse (Ludwig et al., 2018).

Finally, other study confirmed an association between the examined ACEs categories and the lifetime suicide attempts (Berent et al., 2020). Details of the included studies are shown in Table 2.

### 3.5. Association between lifetime trauma exposure and SB

Five studies (Ben-Efraim et al., 2011; Boscarino et al., 2022; Wasserman et al., 2008, 2009; Zhang et al., 2019) reported a significant association of lifetime trauma exposure with suicide behavior, but only two studies (Ben-Efraim et al., 2011; Zhang et al., 2019) used a cross-sectional design with an exposed and control group. Studies were performed on a population with comorbidities, including patients with schizophrenia, bipolar disorder, post-traumatic stress disorder, depression, and substances use.

Suicide attempt was associated with stressful life events in three studies (Ben-Efraim et al., 2011; Wasserman et al., 2008, 2009). Zhang et al., 2009 (Zhang et al., 2019) and Boscarino et al., (2022) (Boscarino et al., 2022) analyzed suicide in the military population who served in Iraq and Afghanistan. Specifically, Zhang et al., 2009 (Zhang et al., 2019) reported a positive association with the SI and stressful life events,

and Boscarino et al., (2022) (Boscarino et al., 2022) indicated that the prevalence of lifetime suicidal thoughts was 11.3% and 5.7%. Furthermore, high lifetime trauma exposure (18.7%), was noteworthy among the veterans and associated with increased likelihood of SB. Details of the included studies are shown in Table 2.

### 3.6. Association between HPA-axis genes and SB

Information of all the candidate gene SNP's included in the study is shown in Table 3. HPA-axis genes studies focused on *FKBP5* (n = 7) and *CRHR1* (n = 7), followed by *CRHR2* (n = 5), *CRH* (n = 3), *CRHBP* (n = 3), *NR3C1* (n = 2), *MC2R* (n = 2), and *POMC* (n = 2).

First, *FKBP5*, an important moderator of NR3C1 sensitivity, was analyzed in seven studies (Ben-Efraim et al., 2011; Berent et al., 2020; Boscarino et al., 2022; Breen et al., 2015; Roy et al., 2010; Segura et al., 2019; Zhang et al., 2019). Four SNP's showed significant associations with the attempted suicide: rs3777747, rs4713902, rs9470080, and rs2766533 (Roy et al., 2010, 2012; Segura et al., 2019). However, some studies did not show the distribution of genotype/allele frequencies, or a negative association was reported (Berent et al., 2020; Boscarino et al., 2022; Breen et al., 2015; Zhang et al., 2019).

Second, seven studies (Ben-Efraim et al., 2011; Boscarino et al., 2022; Guillaume et al., 2013; Ludwig et al., 2018; Sanabrais-Jiménez et al., 2019; Wasserman et al., 2008, 2009) analyzed the association between *CRHR1* SNP's and SB. Four studies reported a positive association with rs4792887, rs12936511, rs242939, rs242938, rs16940665 and the risk of SA (Ludwig et al., 2018; Sanabrais-Jiménez et al., 2019; Wasserman et al., 2008, 2009). Only three studies did not report a risk association (Ben-Efraim et al., 2011; Boscarino et al., 2022; Guillaume et al., 2013).

Third, *CRHBP* was analyzed in three studies (Breen et al., 2015; Roy et al., 2012; Segura et al., 2019), however, only one study reported that rs7728378 SNP could be implicated in the SB (Segura et al., 2019). Finally, single marker analyses indicated a no significant association of *CRH, NR3C1*, *MC2R* and *POMC* with SB (Breen et al., 2015; Guillaume et al., 2013; Roy et al., 2012; Sanabrais-Jiménez et al., 2019; Segura et al., 2019).

### 3.7. The contribution of G × E interaction to SB

As shown in Table 3, 13 studies examined the G × E interaction between trauma exposure and HPA-axis genes focused on suicide behavior (Ben-Efraim et al., 2011; Berent et al., 2020; Boscarino et al., 2022; Breen et al., 2015; Guillaume et al., 2013; Ludwig et al., 2018; Roy et al., 2010, 2012; Sanabrais-Jiménez et al., 2019; Segura et al., 2019; Wasserman et al., 2008, 2009; Zhang et al., 2019). G × E interaction was reported for *CRHR1* (n = 6), *CRHR2* (n = 2), *FKBP5* (n = 2), and *CRHBP* (n = 1). It is important to note that *CRH, NR3C1, MC2R,* and *POMC* genes do not have relationship with the traumatic experiences in the childhood or lifetime trauma exposure.

For *CRHR1*, individual SNP analyses revealed interactions with stressful life events for rs4792887, rs110402, rs242939, rs7209436, rs16940665, rs242948, rs1396862, and rs878886 (Ben-Efraim et al., 2011; Guillaume et al., 2013; Ludwig et al., 2018; Sanabrais-Jiménez et al., 2019; Wasserman et al., 2008, 2009). Interaction *FKBP5* (rs3800373, rs9296158, and rs1360780) or *CRHR2* (rs255098) and childhood trauma was associated with an increased risk of suicide attempt (Guillaume et al., 2013; Roy et al., 2010, 2012; Sanabrais-Jiménez et al., 2019). Moreover, for *CRHBP*, rs6453267, rs7728378 and rs10474485 showed a nominally significant interaction with the continuous CTQ score to predict suicide attempt (Roy et al., 2012).

In addition, G × E interaction has been found to relate to the specific characteristics of the trauma exposure, with associations more evident for maltreatment that occurs at an earlier age. Childhood sexual abuse and emotional neglect may have long-term effects on decision-making through an interaction with *CRHR1* and *CRHR2* (Guillaume et al., 2013). Moreover, genetic variants of *CRHR1* and *CRHR2* genes in addition to physical negligence, and emotional and sexual abuse, contribute to increase risk of presented at least one SA (Sanabrais-Jiménez et al., 2019).

## 4. Discussion

HPA-axis is a key regulator of the response to stress and its dysregulation has been reported in various psychiatric disorders including, suicide. Given the strong association of the trauma exposure with SB, genes that play a role in HPA-axis regulation seem likely candidates to be investigated further. Our study provides a systematic review of epidemiological studies investigating the G × E interaction in the etiology of SB.

We found 13 studies that meet our inclusion criteria. First, all studies reported a positive association between trauma exposure with SB, in particular the childhood trauma and lifetime trauma exposure. Findings from our review showed that the childhood trauma may contribute to greater vulnerability for developing suicide problems later in life.

Our outcomes are in line with previous studies, showing that adults who were exposed to serious trauma were two or three times more likely to development to suicide behavior compared with adults who were not exposed to similar trauma (Beristianos et al., 2016b; Hadland et al., 2015; Spokas et al., 2009). Therefore, adverse experiences confer long-term negative impact on neurodevelopment and neurobiological functions, further contributing to the risk of suicide in the adulthood (Alter et al., 2021; Beristianos et al., 2016a).

Second, we proposed enlisting *CRHR1*, *CRHR2*, *FKBP5*, and *CRHBP* as possible mediators of the relationship between trauma exposure and SB. The diathesis-stress model of the suicidal behavior claims that trauma exposure and genes may be distal predictors of suicide, creating vulnerability to adverse factors appearing later in life (Chasiropoulou et al., 2019; Eisenlohr-Moul et al., 2018). For instance, Roy et al., (2010) (Roy et al., 2010) reports that significant interaction between the childhood trauma and *FKBP5* (rs3800373, rs9296158, and rs1360780) raise the risk of suicide attempt. Tyrka et al. (2009) indicated that variations in *CRHR1* (rs110402 and rs242924) moderates the effect of childhood maltreatment on cortisol (stress hormone) responses to the DEX/CRH test. Moreover, genome-wide (GWAS) analyses have identified 14 independent loci for the childhood maltreatment. The GWAS signal was enriched for regulatory chromatin marks in brain tissues and for genes that are highly expressed in excitatory neurons (Warrier et al., 2021).

We suggest that trauma exposure could be one mechanism that links HPA-axis genes activity with the development of SB. Notably, the HPA-axis genes are regulated via complex interactions among trauma exposure, genetic variants, and possibly epigenetic modifications (Ramos-Rosales et al., 2021; Wasserman et al., 2010). Allele-specific epigenetic modifications that regulate the transcription levels or genes expression have been reported in stress-related psychiatric disorders (Klengel and Binder, 2013; Klengel et al., 2014). Therefore, SNP's can create a molecular background of susceptibility to an adverse environment or may also create susceptibility to a beneficial environment if one is born in supportive milieu or translocated from an unsupportive environment in early childhood (Kim and Lee, 2016; Normann and Buttenschøn, 2020). These interactions may regulate the expression of genes involved in stress responses and other vias, contributing to vulnerability/resilience endophenotypes and, a continuum of phenotypes ranging from suicide ideation to die by suicide (Courtet et al., 2011). This model of regulation is described in more detail and presented schematically in Fig. 2.

Third, it is important to note that, *CRH, NR3C1, MC2R, and POMC* genes do not have relationship with the traumatic experiences in the childhood or lifetime trauma exposure. Lack of evidence for G x E associations with SB in the studies might be caused by a lack of statistical power. However, a role for epigenetic in the relationship between HPA-

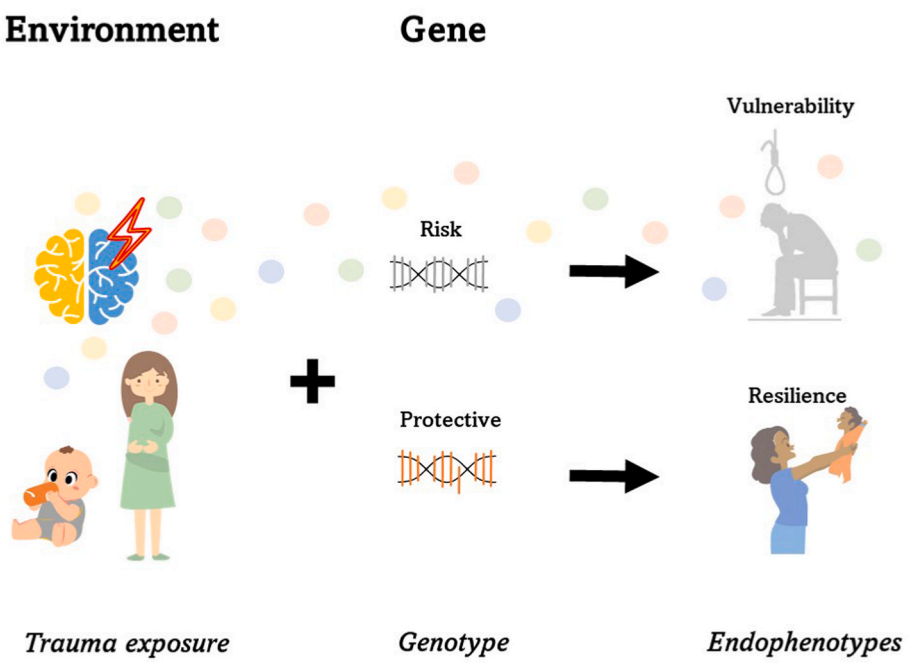


**Fig. 2.** Simplified schematic representation of gene-trauma interactions in the suicide behavior and related phenotypes.

axis and SB has been reported (Jokinen et al., 2018; McGowan et al., 2009). Therefore, epigenetic and genetic features of the HPA-axis genes may provide more significant interactions.

Meta-analysis and meta-regression of case-control studies have analyzed the interactions between HPA-axis genes variants and early-life stress on the risks of psychiatric disorders. Bipolar disorder, major depressive disorder, and post-traumatic stress disorder have been associated with dysfunction of HPA-axis activity, with important pathophysiological implications (Belvederi Murri et al., 2016; Sheerin et al., 2020; Wang et al., 2018).

The results of the present study reveal important clinical implications. First, the findings emphasize the importance of integrating a history of early childhood abuse data. Moreover, it is plausible that exposure to the childhood abuse increases levels of circulating biomarkers which in turn trigger the development of SB. Indeed, studies have suggested the increase in pro-inflammatory cytokines and cortisol (Hernández-Díaz et al., 2020; Melhem et al., 2017). Consequently, it is important investigate the association between the childhood abuse and biomarkers in a population representative sample. Second, the findings may help us to better understand how environmental exposures, interact with genetic factors to shape long-term trajectories of contributing to the risk of suicide in the adulthood and the healthcare providers guide the suicide behavior screening efforts.

There are some limitations to be noted regarding this review. Studies varied in the populations sampled and methods used to assess trauma exposure. Finally, sample sizes and the number of investigated variants could be low to detect small effects.

In conclusion, our systematic review showed that individuals with trauma exposure may have long-term effects that may contribute to greater vulnerability for developing suicide behavior. We found that variants in *FKBP5, CRHR1, CRHR2, CRHBP,* and *POMC* genes and the trauma exposure could increase the susceptibility to suicide behavior.

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## Declaration of competing interest

The authors declare that there is no confict of interest.

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