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# Childhood Trauma increases suicidal behaviour in a treatment-resistant depression population: a FACE-DR report

## Running title: Childhood Trauma and suicidal behaviour

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## **Abstract**

**Objective:** In addition to heredity, exposure to early-life adversity is an important predisposing risk factor of suicidal behaviour. Although the association between Childhood Trauma (CT) and suicide risk is well documented, interactions between CT and suicidal behaviour in Treatment-Resistant Depression (TRD) populations have received little coverage. This study aimed to evaluate i) association between CT and suicidal behaviour in a TRD population, and ii) the role of personality traits and impulsiveness as potential factors of mediation in these associations.

**Methods:** Patients were recruited from a cohort of the French network of TRD expert centers. Depressive symptom severity, CT, suicidal behaviour, personality traits, and impulsiveness were assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS), the Childhood Trauma Questionnaire (CTQ), the Columbia Suicide Severity Rating Scale (CSSRS), the Structured Clinical Interview for DSM-IV, the Big Five Inventory, and the Barratt Impulsiveness Scale (BIS) respectively.

**Results:** Among the 256 patients with a baseline CTQ, in relation to suicide risk for the current depressive episode, we found an association with the total CTQ scores mediated by the intensity of the current episode in a model adjusted for age and sex (total effect:  $\beta=0.171$ ;  $p=0.011$ , direct effect:  $\beta=0.135$ ;  $p=0.043$ ; indirect effect:  $\beta=0.036$ ;  $p=0.048$ ). Focusing on CT subtypes, we detected an association between suicide risk and physical neglect in a model adjusted for age and sex ( $\beta=0.301$ ;  $p=0.002$ ), without any mediation by the intensity of the current episode. There was no mediation effect from personality traits nor impulsiveness. With regards to CSSRS to assess suicidal ideation, we did not find any association with the total CTQ score and CT subtype scores.

**Conclusion:** We report a strong association between suicidal behaviour and CT (in particular childhood physical neglect) in a TRD population.

**Keywords:** Childhood Trauma; Childhood Abuse; Childhood neglect; Treatment-Resistant Depression; Suicide; Depressive Disorders.

## **Introduction**

Over 800,000 people die of suicide worldwide each year (WHO, 2014), with non-fatal suicidal behaviour substantially outnumbering suicide deaths (Borges et al., 2010; Nock et al., 2013; Turecki & Brent, 2016). The worldwide lifetime prevalence of suicidal ideation and suicide attempts is 9.2% and 2.7%, respectively (Nock et al., 2008; Turecki & Brent, 2016). Individuals who report suicidal ideations within the last 12 months have significantly higher suicide rates achieving between 15% and 20% (Borges et al., 2010; Nock et al., 2013; Turecki & Brent, 2016). Data from emergency departments indicate that people attempting suicide have a 1.6% risk of dying by suicide within the year, and a 16% risk of attempting suicide again with a 5-year suicide risk of around 4% (Carroll et al., 2014).

Most models of suicide risk emphasise the interaction between predisposing and precipitating factors (Turecki & Brent, 2016). Mood disorders are among the most frequent psychiatric disorders contributing to suicide attempts (Georgiades et al., 2019; Nock et al., 2009; Turecki & Brent, 2016). Major Depressive Disorder (MDD) is one of most significant precipitating factors (Turecki et al., 2019). Furthermore, patients experiencing Treatment-Resistant Depression (TRD) are more likely to report a prior suicide attempt compared to individuals showing a favorable treatment response, and treatment resistance rates are higher in patients with severe suicidality (Dold et al., 2018; Malhi et al., 2005; Nelsen & Dunner, 1995). It is reported that approximately 30% of patients with TRD attempt suicide at least once in their lifetime (Dunner et al., 2006; Hantouche et al., 2010; Ozcan et al., 2020). This rate is reported to be at least twice the lifetime suicide rate in patients with non-resistant depression (Bernal et al., 2007; Chen & Dilsaver, 1996).

Among predisposing factors, heredity seems to play an important role. The risk of attempted suicide is 2.0 to 4.8 times higher in relatives of individuals who have died by suicide, and 2 to

7.6 times higher in relatives of individuals with a history of suicide attempts (Brent & Melhem, 2008). Genetic factors appear to be pivotal in the familial transmission of suicidal behaviour with an estimated heritability ranging from 30% to 50% (Turecki & Brent, 2016). Another predisposing risk factor is exposure to early-life adversity such as parental neglect or childhood physical, sexual, and emotional abuse (Castellví et al., 2017). The association between Childhood Trauma (CT) and lifetime suicide risk is well established (Afifi et al., 2008; Brezo et al., 2008; Fergusson et al., 2000a). Several studies report strong associations of childhood sexual abuse with *i*) suicidal ideation, and *ii*) suicidal behaviour (Gomez et al., 2017; Hooven et al., 2012; A. B. Miller et al., 2013; Sit et al., 2015). Physical and emotional abuse is also associated with a high risk of suicidal behaviour (Gomez et al., 2017; Janiri et al., 2018). Moreover, sexual and physical abuse have been closely linked with repeated suicide attempts, independently of other trauma subtypes (emotional abuse and neglect, and physical neglect) (Ystgaard et al., 2004). In a recent meta-analysis, it has been highlighted that all different types of childhood maltreatment were associated with a two- to three-fold increased risk of suicide attempts and suicidal ideation (Angelakis et al., 2019).

Furthermore, CT not only increases the risk of suicide but also precipitates the development of MDD throughout the lifespan, and aggravates its course and chronicity (Bernet & Stein, 1999; Brown et al., 2007; C. Heim & Nemeroff, 2001; Hovens et al., 2010; Liu et al., 2009; Nanni et al., 2012; Wainwright & Surtees, 2002; Wiersma et al., 2009). We highlighted a significant association between CT, mainly regarding physical abuse/neglect, and clinical severity in the TRD population (Yroni et al., 2020). Moreover, intensity of MDD episode was found to be linked to suicide (McGirr et al., 2008; Turecki et al., 2019).

Key mediating factors between predisposing factors and precipitating factors include personality traits. Among these, those most robustly associated with suicidal behaviour are impulsive-aggressive traits (Fergusson et al., 2000b; Mann et al., 2009; Turecki et al., 2019).

Behavioural disinhibition and impulsiveness have been extensively reported to encourage suicidal behaviours (Carpiniello et al., 2011; Corruble et al., 2003; Ponsoni et al., 2018). Furthermore, individuals who have experienced CT have a greater risk of developing pathological traits and emotional dysregulation thereby increasing the vulnerability to suicide (Turecki et al., 2019).

However, there is little data available focusing on the mediating role of personality traits, impulsiveness, and depressive symptom severity in the relationships between CT and suicidal ideation and behaviours in the specific context of TRD. Indeed, to our knowledge, only one study by Tunnard et al. (2014) has to date documented an association between CT and repeated suicide attempts in a large sample of TRD patients. However, this study did not assess mediating factors or suicidal ideation.

### ***Aims of the study***

This study aims to evaluate any potential associations between CT, including different subtypes of trauma, and *i*) suicide attempts, *ii*) suicide risk, and *iii*) suicidal ideation in a TRD population, and the potentially mediating role of personality traits, impulsiveness, and depressive symptoms severity.

## **Methods**

### ***Population***

Patients were recruited from a cohort (FACE-DR cohort) of the French network of expert centers for TRD, consisting of 13 specialty care centers located in academic psychiatry departments throughout France (Yroni et al., 2017).

The patients selected were clinically unresponsive to at least two successive courses of antidepressants from two different pharmacological classes, corresponding to at least stage II of the TRD staging criteria defined by Thase & Rush (Thase & Rush, 1997). At inclusion, all



the patients were treated with an antidepressant medication. Before participating in the full assessment, patients were interviewed by a psychiatrist at the expert center in order to:

- Confirm the diagnosis of MDD according to the DSM-IV (MINI) (Frances et al., 2000) criteria with moderate to severe symptoms, as attested by the Montgomery and Åsberg Rating Scale (MADRS) and a total score above 20 (Taylor et al, 2006), and the level of resistance indicated by, both, the classification of Thase & Rush  $\geq 2$  (Thase & Rush, 1997) and Antidepressant Treatment History Form (ATHF) (Sackeim, 2001)
- Exclude bipolar disorders, psychotic disorders, obsessive-compulsive disorders, eating disorders (with BMI < 15), somatoform disorders, and mood disorders related to substance abuse or misuse.
- Inform the patient about the formal assessment procedure.

### ***Assessment***

For this study, we focused on assessments performed at baseline, after inclusion of TRD patients. Severity of depressive symptoms was assessed with the MADRS (Montgomery & Asberg, 1979). The inter-rater reliability of the MADRS scale was high. Scores on the scale correlated significantly with scores on a standard rating scale for depression, the Hamilton Rating Scale, indicating its validity as a general estimate of severity (Montgomery & Asberg, 1979).

Childhood Trauma was evaluated with the Childhood Trauma Questionnaire (CTQ) based on five major trauma subtypes: emotional abuse (EA)(None:5-8, Low:9-12, Moderate: 13-15, Severe:16+), physical abuse (PA) )(None:5-7, Low:8-9, Moderate: 10-12, Severe:13+), sexual abuse (SA) (None:5, Low:6-7, Moderate: 8-12, Severe:13+), emotional neglect (EN) )(None:5-9, Low:10-14, Moderate: 15-17, Severe:18+), and physical neglect (PN) (None:5-7,

Low:8-9, Moderate: 10-12, Severe:13+) (Bernstein et al., 1994). Bernstein et al. (1994) highlighted that the CTQ has strong reliability and validity.

Suicide is defined as intentionally ending one's own life, a suicide attempt as self-injurious, non-fatal behaviour with inferred or actual intent to die, and suicidal behaviours as those which may result in ending one's own life, whether fatal or not. This term excludes suicidal ideation. Suicidal ideations are defined as any thoughts about ending one's own life. The risk of acting on suicidal thoughts increases with the frequency, intent, and content of suicidal ideation (Turecki et al., 2019). Suicide risk was assessed with the Structured Clinical Interview for DSM-IV (MINI) (First et al., 2016). A suicidal ideation score is derived from the Columbia Suicide Severity Rating Scale (CSSRS) by adding the severity and intensity sub-scores (Ducasse et al., 2014; Posner et al., 2011). The CSSRS demonstrated good convergent and divergent validity with other multi-informant suicidal ideation and behaviour scales and had high sensitivity and specificity for suicidal behaviour classifications compared with another behaviour scale and an independent suicide evaluation board. Both the ideation and behaviour subscales were sensitive to change over time. The intensity of ideation subscale demonstrated moderate to strong internal consistency (Posner et al., 2011).

Personality traits were assessed with the Big Five Inventory (BFI) (Goldberg, 1990). It assessed five personality traits (neuroticism, extraversion, agreeableness, openness and conscientiousness). The mean internal consistency (0.79) is excellent, providing clear evidence of the psychometric qualities of the tool (internal validity). Internal consistencies of the five personality dimensions were comparable for the BFI and the Revised NEO Personality Inventory (Neuroticism, Extraversion and Openness; NEO-PI-R) (Plaisant et al., 2010).

Impulsiveness was assessed with the Barratt Impulsiveness Scale (BIS) (Patton et al., 1995). Two of the three subtests of the BIS-11 (motor and non-planning) are consistent with those

originally hypothesized by Barratt (Barratt, 1985), but no “pure” cognitive impulsiveness component was evident. The BIS-11 total score was internally consistent across populations and has potential clinical utility for measuring impulsiveness among selected patient and inmate populations.

This assessment protocol was approved by the institutional review board (French CNIL: DR-2015-673) in accordance with French law for non-interventional studies, and requires only an information letter.

### *Statistics*

Sociodemographic and clinical characteristics were presented using means and standard deviations for continuous variables and frequency distributions for categorical variables. First, Linear regression models (enter method) were applied to test the association between dependent variables such as MINI suicide score, CSSRS, and independent variables: CTQ and CT subtypes. We also assessed association between those previous variables and potential mediation factors [depression intensity (MADRS score), personality traits (BFI) and impulsiveness (BIS-11)]. Second, a GLM (general linear model) mediation model (Gallucci, 2019; Rosseel, 2012) was used to assess the association between CTQ and CT subtype (independent variable) and dependent variables such as MINI suicide score and CSSRS. The potential mediation factors showing an association were added in this model. The independent variables are all considered parallel independent variables. The mediators are all inserted in the model as parallel mediators. Mediators were referred to as the related factors that could be used to explain the observed relationship between an exposure variable and an outcome. The exposure variable is CT and the outcome is suicidal behaviour. The GLM mediation model was adjusted based on age and sex. We compared data from patients who did not fill out the CTQ with our sample using the t-test for continuous variables and the Chi2 for categorical

variables. We used one-way ANOVA to compare groups. Statistical analyses were performed with Jamovi 1.2 (R Core Team, 2019; The jamovi project, 2020)

## **Results**

### ***Demographic data***

The FACE-DR cohort enrolled 291 patients between 2012 and 2018. Of these, 256 patients (87.7%) had filled out the CTQ at baseline and 91 individuals (31.3%) in this group had attempted suicide prior to baseline. The mean age was 53.21 (SD=12.93) and 62.3% were female. The mean MADRS score was 28.92 (SD=6.90). For emotional abuse, 2.7% of the population had severe intensity and 2% moderate intensity. For physical abuse, 48.8% presented severe intensity and 19.9% moderate intensity. With regard to sexual abuse, 6.6% had a severe score and 33.6% a moderate score. Regarding emotional neglect, the severe and moderate intensities represented 2.7% each, while 25.8% presented severe intensity and 14.5% moderate intensity for physical neglect. The overall characteristics of these 256 patients are summarized in Table 1. We did not find any difference in clinical features between patients who filled out the CTQ and those who did not (Table 2)

### ***Associations between Childhood Trauma and suicidal behaviour in the TRD cohort***

With regard to CSSRS to assess suicidal ideation, we did not find any association with total CTQ score ( $\beta=0.042$ ;  $p=0.564$ ) and CT subtype scores (EA score:  $\beta=0.16$ ;  $p=0.084$ ; PA score:  $\beta=0.057$ ;  $p=0.573$ ; SA score:  $\beta=-0.11$ ;  $p=0.193$ ; EN score:  $\beta=-0.053$ ;  $p=0.506$ ; PN score:  $\beta=-0.02$ ;  $p=0.852$ ). However, in relation to suicide risk using the MINI suicide score for the current depressive episode, we found an association with the total CTQ scores mediated by the intensity of the current episode (MADRS score) (Table 3) in a model adjusted for age and

sex (total effect:  $\beta=0.171$ ;  $p=0.011$ , direct effect:  $\beta=0.135$ ;  $p=0.043$ ; indirect effect:  $\beta=0.036$ ;  $p=0.048$ ) (Figure 1).

Focusing on CT subtypes, we did not find any significant association between the MINI suicide score and the scores of the different CT subtypes such as EA score, PA score, SA score or EN score (EA:  $\beta=-0.063$ ;  $p=0.489$ ; PA:  $\beta=-0.06$ ;  $p=0.522$ ; SA:  $\beta=-0.003$ ;  $p=0.971$ ; EN:  $\beta=0.03$ ;  $p=0.742$ ). However, we observed a strong association between the MINI suicide score and the physical neglect score in a model adjusted for age and sex ( $\beta=0.301$ ;  $p=0.002$ ), without any mediation by the intensity of the current episode (MADRS score) (Table 4; Figure 2).

### ***Assessment of factors mediating the association between Childhood Trauma and suicidal behaviour in the TRD cohort***

We examined the putative mediating role of critical factors such as personality traits and impulsiveness in the relationships between CT and suicide risk in our TRD population.

#### *Associations between Childhood Trauma, suicide risk/behaviour, and personality traits in TRD*

We found no significant association between CT and personality traits, namely neuroticism ( $\beta=0.117$ ;  $p=0.085$ ), extraversion ( $\beta=-0.054$ ;  $p=0.41$ ), agreeableness ( $\beta=0.023$ ;  $p=0.73$ ), openness ( $\beta=-0.002$ ;  $p=0.98$ ), and conscientiousness ( $\beta=0.041$ ;  $p=0.55$ ). This supports that we could not use a mediation model to assess whether personality traits mediated any relationship between CT and (i) suicide risk and (ii) suicidal behaviour (Supplementary Material S1).

#### *Associations between Childhood Trauma, suicide risk/behaviour, and impulsiveness in TRD*

We did not find any significant association between impulsiveness (BIS) and CT or CT subtypes (CTQ:  $\beta=0.079$ ;  $p=0.233$ ; EA score:  $\beta=0.108$ ;  $p=0.51$ ; PA score:  $\beta=0.085$ ;  $p=0.98$ ;

SA score:  $\beta=0.054$ ;  $p=0.999$ ; EN score:  $\beta=0.053$ ;  $p=0.999$ ; PN score:  $\beta=0.012$ ;  $p=0.999$ ). This supports that a mediation model could not be used to assess whether impulsiveness mediated any relationship between CT and (i) suicide risk and (ii) suicidal behaviour.

## **Discussion**

To our knowledge, our study is the first to specifically investigate associations between childhood adversities and suicidal risk and ideation in a TRD population.

Regarding suicide risk, we showed that depressive symptoms (MADRS) significantly mediated the effect of CT on suicide risk. However, when suicidal ideation was assessed with CSSRS, we did not observe any association with CT (or subtypes). Finally, there was no relationship between CT and *i*) personality traits and *ii*) impulsiveness.

In terms of the TRD literature, our results are in line with those reported by Tunnard et al. showing that CT was associated with an increased risk of suicidal behaviours (Tunnard et al., 2014). In addition, we specifically found an association between childhood physical neglect and suicide risk. However, our findings are not consistent with the previously published studies on non-resistant MDD documenting that physical abuse, sexual abuse, and emotional abuse are associated with an increased risk of suicidal behaviour (Gomez et al., 2017; Hooven et al., 2012; Janiri et al., 2018; A. B. Miller et al., 2013; Ystgaard et al., 2004). Moreover, Norman's meta-analysis supported a clear relationship between physical abuse and emotional abuse and neglect with suicidal behaviour (Norman et al., 2012). Surprisingly, in relation to impulsiveness, which is a well-established risk factor for suicide, our results were not consistent with those of Brodsky et al. reporting that patients with a childhood history of abuse had significantly higher impulsiveness and aggression scores than those who did not report any previous history of abuse (Brodsky et al., 2001). Moreover, while Zhang et al. have shown that personality traits could be potential mediators in the relationships between CT and

depressive symptoms, we did not find any association between CT and personality profiles (Zhang et al., 2018). In our study, personality traits and impulsiveness were not reported to mediate the influence of CT on suicidal behaviour and risk. This may be due to the fact that TRD participants were currently treated with antidepressant medication which could improve impulsiveness and change personality components although having no significant effect on overall clinical severity (Bond, 2005; Jylhä et al., 2020).

To summarize, we report strong associations between CT (mainly physical neglect) with suicidal risk in the TRD population. This could be explained by the pathophysiology of TRD and biological mechanisms related to Childhood Trauma. The hypothalamic-pituitary-adrenal (HPA) axis regulates physiological responses to stress and allows individuals to cope with a changing environment or specific events by regulating cortisol levels (Lutz et al., 2017; Turecki & Brent, 2016). Individuals who experience early-life adversity often have a overactive HPA axis and an increased stress response (Christine Heim et al., 2010). This is partly due to lowered hippocampal expression of glucocorticoid receptors (GRs) caused by increased receptor promoter methylation in both central nervous and peripheral tissues (McGowan et al., 2009; Turecki & Meaney, 2016). CT was recently demonstrated to be associated with elevated peripheral concentrations of pro-inflammatory cytokines (Coelho et al., 2011, 2014; Müller et al., 2019). Moreover, MDD and TRD appear to be related to dysfunction of the immune and inflammatory responses (A. H. Miller & Raison, 2016). In the context of MDD, external stress can be a precipitating factor, which can increase levels of circulating cytokines (TNF $\alpha$  and IL-6), both peripherally and systemically (A. H. Miller, 2009; A. H. Miller et al., 2009). Increased expression of these central nervous system (CNS) cytokines appears to result from activation of the microglia by external stress factors (A. H. Miller et al., 2009). Proinflammatory cytokines contribute to the overactive HPA axis observed in MDD. These cytokine changes also alter the metabolism of serotonin,

norepinephrine, and dopamine in brain regions essential for regulating emotions and behaviours, such as the limbic system (amygdala, hippocampus, and nucleus accumbens) (Raison et al., 2006). Indeed, inflammation has largely been documented to generate brain monoamine deficits (Raison et al., 2006). Furthermore, the impairment of the serotonin, norepinephrine, and dopamine pathways is pivotal in precipitating MDD and/or suicidal behaviour (Belmaker & Agam, 2008; Lutz et al., 2017). In addition, monoaminergic, inflammatory, and immune pathways underpin the mechanisms of TRD. Antidepressant treatments that primarily target monoamine transmissions are presumably unable to compensate for the monoamine deficit generated by inflammatory conditions (Capuron & Auouizerate, 2017; Capuron & Miller, 2011; Coplan et al., 2014; Lutz et al., 2017; A. H. Miller et al., 2009). Taken together, these observations plead for the pivotal role of these biological pathways in the relationships between CT and suicidal behaviour and suicide risk in the TRD population.

### *Limitations*

Our cohort excluded mood disorders related to substance abuse and/or misuse, even though substance abuse/misuse is a major suicide risk factor (Turecki & Brent, 2016). This exclusion may underestimate the association between CT and suicide risk and/or suicidal behaviour in our study. In addition, we only assessed suicidal ideation with CSSRS at a single point in time. A more complex assessment based on measurements at regular time intervals would be informative to detect any potential associations between CT and suicidal ideation over time. Moreover, the CTQ asks questions retrospectively, which could induce a memory bias. Finally, we did not take into account any of the biological mechanisms that are thought to underpin the associations between CT and suicidal behaviour and suicide risk in TRD.



## **Conclusion**

Here, we found a significant association between suicidal behaviour and Childhood Trauma, predominantly with respect to physical neglect, in our TRD population. This is consistent with the previously reported relationships between CT and suicidal behaviour in MDD populations. In clinical practice, information about a history of childhood abuse could therefore help to identify individuals at risk of suicidal behaviour. However, the significance of our findings would need to be confirmed in a larger prospective TRD cohort designed to evaluate suicide attempts in relation to biological assessments including especially HPA axis-immune functions. Better characterization and understanding of the clinical and biological features involved in TRD, through a better determination of the long-term impact of CT for the early identification and efficient prevention of suicidal behaviour, may uncover useful parameters for mental health providers in everyday clinical practice.

## **Data Availability Statement**

To get the available data, please contact the corresponding author:

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All authors have approved the manuscript.

## **Conflict of interest statement**

Antoine Yroni received speaker's honoraria (AstraZeneca, Janssen, Lundbeck, Otsuka, Servier) and carried out clinical studies in relation to the development of a medicine (Janssen, Lundbeck) unrelated to this work.

Olivier Doumy received honoraria from Lilly, Astra-Zeneca, Janssen, Servier, and Lundbeck.

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Raphael Richieri received a speaker's honorarium from Janssen Cilag.

Ludovic Samalin received grants, honoraria, and consulting fees from Janssen-Cilag, Lundbeck, and Otsuka.

Florian Stephan received honoraria from Otsuka.

Emmanuel Haffen: acted in advisory capacities, carried out clinical studies in relation to the development of a medicine, received personal researches, studies, or travel allowance, gave presentations at meetings, and received remuneration for input from the following pharmaceutical organisations: AstraZeneca, BMS, Cellgene, Euthérapie - Servier, Janssen, Elli Lilly, Lundbeck, LivaNova, Otsuka, Pfizer, Sanofi. He also held a managerial position in the FondaMental Foundation (Créteil) and the French Association of Biological Psychiatry and Neuropsychopharmacology.

Wissam El-Hage reports receiving speaker's honoraria from Chugai, Eisai, Lundbeck, Janssen-Cilag, Otsuka, and UCB unrelated to this work.

Bruno Aouizerate: received speaker's honoraria and/or a travel allowance from Lundbeck, Janssen-Cilag, and Eli Lilly. He has served on the advisory board of Janssen-Cilag.

Thierry d'Amato, Franck Bellivier, Djamila Bennabi, Thierry Bougerol, Vincent Camus, Philippe Courtet, Jérôme Holtzmann, Christophe Lançon, Marion Leboyer, Julia Maruani, Rémi Moirand, Fanny Molière, Michel Walter Jean Petrucci, Laurent Schmitt and Guillaume Vaiva declare having no conflicts of interest.

**Contributions:** All authors were involved in the identification and selection of patients, in the clinical assessment, and co-wrote the paper. A. Yroni, G. Vaiva, M. Walter, P. Courtet, W. El-Hage, and B. Aouizerate were also involved in choosing the data set for this project and the statistical analysis.

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**Ethical standards:** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

## References

- Afifi, T. O., Enns, M. W., Cox, B. J., Asmundson, G. J. G., Stein, M. B., & Sareen, J. (2008). Population attributable fractions of psychiatric disorders and suicide ideation and attempts associated with adverse childhood experiences. *American Journal of Public Health, 98*(5), 946-952. <https://doi.org/10.2105/AJPH.2007.120253>
- Angelakis, I., Gillespie, E. L., & Panagioti, M. (2019). Childhood maltreatment and adult suicidality : A comprehensive systematic review with meta-analysis. *Psychological Medicine, 49*(7), 1057-1078. <https://doi.org/10.1017/S0033291718003823>
- Barratt, E. S. (1985). BARRATT, E. S. (1985). Impulsiveness subtraits : Arousal and information processing. In J. T. Spence & C. E. hard (Eds.), *Mofivation, emotion, andpersonality* (pp. 137-146). North-Holland : Elsevier Science. In *Motivation, emotion, and personality* (J. T. Spence&C. E. hard, p. 137-146). Elsevier Science.
- Belmaker, R. H., & Agam, G. (2008). Major depressive disorder. *The New England Journal of Medicine, 358*(1), 55-68. <https://doi.org/10.1056/NEJMra073096>
- Bernal, M., Haro, J. M., Bernert, S., Brugha, T., de Graaf, R., Bruffaerts, R., Lépine, J. P., de Girolamo, G., Vilagut, G., Gasquet, I., Torres, J. V., Kovess, V., Heider, D., Neeleman, J., Kessler, R., Alonso, J., & ESEMED/MHEDEA Investigators. (2007). Risk factors for suicidality in Europe : Results from the ESEMED study. *Journal of Affective Disorders, 101*(1-3), 27-34. <https://doi.org/10.1016/j.jad.2006.09.018>
- Bernet, C. Z., & Stein, M. B. (1999). Relationship of childhood maltreatment to the onset and course of major depression in adulthood. *Depression and Anxiety, 9*(4), 169-174. [https://doi.org/10.1002/\(SICI\)1520-6394\(1999\)9:4<169::AID-DA4>3.0.CO;2-2](https://doi.org/10.1002/(SICI)1520-6394(1999)9:4<169::AID-DA4>3.0.CO;2-2)
- Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., & Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American Journal of Psychiatry, 151*(8), 1132-1136. <https://doi.org/10.1176/ajp.151.8.1132>
- Borges, G., Nock, M. K., Haro Abad, J. M., Hwang, I., Sampson, N. A., Alonso, J., Andrade, L. H., Angermeyer, M. C., Beautrais, A., Bromet, E., Bruffaerts, R., de Girolamo, G., Florescu, S., Gureje, O., Hu, C., Karam, E. G., Kovess-Masfety, V., Lee, S., Levinson, D., ... Kessler, R. C. (2010). Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. *The Journal of Clinical Psychiatry, 71*(12), 1617-1628. <https://doi.org/10.4088/JCP.08m04967blu>
- Brent, D. A., & Melhem, N. (2008). Familial transmission of suicidal behavior. *The Psychiatric Clinics of North America, 31*(2), 157-177. <https://doi.org/10.1016/j.psc.2008.02.001>
- Brezo, J., Paris, J., Vitaro, F., Hébert, M., Tremblay, R. E., & Turecki, G. (2008). Predicting suicide attempts in young adults with histories of childhood abuse. *The British Journal of Psychiatry: The Journal of Mental Science, 193*(2), 134-139. <https://doi.org/10.1192/bjp.bp.107.037994>
- Brodsky, B. S., Oquendo, M., Ellis, S. P., Haas, G. L., Malone, K. M., & Mann, J. J. (2001). The relationship of childhood abuse to impulsivity and suicidal behavior in adults with major depression. *The American Journal of Psychiatry, 158*(11), 1871-1877. <https://doi.org/10.1176/appi.ajp.158.11.1871>
- Brown, G. W., Craig, T. K. J., Harris, T. O., Handley, R. V., & Harvey, A. L. (2007). Development of a retrospective interview measure of parental maltreatment using the Childhood Experience of Care and Abuse (CECA) instrument—A life-course study of adult chronic depression—1. *Journal of Affective Disorders, 103*(1), 205-215. <https://doi.org/10.1016/j.jad.2007.05.022>
- Capuron, L., & Auouizerate, B. (2017). Immunoinflammation in psychiatric diseases : What

leads? *La Revue Du Praticien*, 67(9), 950-952.

Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling : Neuropsychopharmacological implications. *Pharmacology & Therapeutics*, 130(2), 226-238. <https://doi.org/10.1016/j.pharmthera.2011.01.014>

Carpiniello, B., Lai, L., Pirarba, S., Sardu, C., & Pinna, F. (2011). Impulsivity and aggressiveness in bipolar disorder with co-morbid borderline personality disorder. *Psychiatry Research*, 188(1), 40-44. <https://doi.org/10.1016/j.psychres.2010.10.026>

Carroll, R., Metcalfe, C., & Gunnell, D. (2014). Hospital presenting self-harm and risk of fatal and non-fatal repetition : Systematic review and meta-analysis. *PloS One*, 9(2), e89944. <https://doi.org/10.1371/journal.pone.0089944>

Castellví, P., Miranda-Mendizábal, A., Parés-Badell, O., Almenara, J., Alonso, I., Blasco, M. J., Cebrià, A., Gabilondo, A., Gili, M., Lagares, C., Piqueras, J. A., Roca, M., Rodríguez-Marín, J., Rodríguez-Jimenez, T., Soto-Sanz, V., & Alonso, J. (2017). Exposure to violence, a risk for suicide in youths and young adults. A meta-analysis of longitudinal studies. *Acta Psychiatrica Scandinavica*, 135(3), 195-211. <https://doi.org/10.1111/acps.12679>

Chen, Y. W., & Dilsaver, S. C. (1996). Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biological Psychiatry*, 39(10), 896-899. [https://doi.org/10.1016/0006-3223\(95\)00295-2](https://doi.org/10.1016/0006-3223(95)00295-2)

Coplan, J. D., Gopinath, S., Abdallah, C. G., & Berry, B. R. (2014). A neurobiological hypothesis of treatment-resistant depression—Mechanisms for selective serotonin reuptake inhibitor non-efficacy. *Frontiers in Behavioral Neuroscience*, 8, 189. <https://doi.org/10.3389/fnbeh.2014.00189>

Corruble, E., Benyamina, A., Bayle, F., Falissard, B., & Hardy, P. (2003). Understanding impulsivity in severe depression? A psychometrical contribution. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 27(5), 829-833. [https://doi.org/10.1016/S0278-5846\(03\)00115-5](https://doi.org/10.1016/S0278-5846(03)00115-5)

Dold, M., Bartova, L., Fugger, G., Kautzky, A., Souery, D., Mendlewicz, J., Papadimitriou, G. N., Dikeos, D., Ferentinos, P., Porcelli, S., Serretti, A., Zohar, J., Montgomery, S., & Kasper, S. (2018). Major Depression and the Degree of Suicidality : Results of the European Group for the Study of Resistant Depression (GSRD). *The International Journal of Neuropsychopharmacology*, 21(6), 539-549. <https://doi.org/10.1093/ijnp/pyy009>

Ducasse, D., René, E., Béziat, S., Guillaume, S., Courtet, P., & Olié, E. (2014). Acceptance and commitment therapy for management of suicidal patients : A pilot study. *Psychotherapy and Psychosomatics*, 83(6), 374-376. <https://doi.org/10.1159/000365974>

Dunner, D. L., Rush, A. J., Russell, J. M., Burke, M., Woodard, S., Wingard, P., & Allen, J. (2006). Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *The Journal of Clinical Psychiatry*, 67(5), 688-695.

Fergusson, D. M., Woodward, L. J., & Horwood, L. J. (2000a). Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychological Medicine*, 30(1), 23-39.

Fergusson, D. M., Woodward, L. J., & Horwood, L. J. (2000b). Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychological Medicine*, 30(1), 23-39.

First, M. B., Williams, J., Karg, R., & Spitzer, R. L. (2016). *Structured Clinical Interview for DSM-5 (SCID-5)* (American Psychiatric Association).

Frances, A., Pincus, H. A., & First, M. B. (2000). *AMERICAN PSYCHIATRIC ASSOCIATION DSM-IV-TR* (4ème édition texte révisé). <http://dsm.psychiatryonline.org/content.aspx?bookid=22&sectionid=1890370>

Gallucci, M. (2019). *jAMM: jamovi Advanced Mediation Models. [Jamovi module]*. Retrieved from <https://jamovi-amm.github.io/>.

Georgiades, K., Boylan, K., Duncan, L., Wang, L., Colman, I., Rhodes, A. E., Bennett, K., Comeau, J., Manion, I., Boyle, M. H., & 2014 Ontario Child Health Study Team. (2019). Prevalence and Correlates of Youth Suicidal Ideation and Attempts : Evidence from the 2014 Ontario Child Health Study. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, 64(4), 265-274. <https://doi.org/10.1177/0706743719830031>

Goldberg, L. R. (1990). An alternative « description of personality » : The big-five factor structure. *Journal of Personality and Social Psychology*, 59(6), 1216-1229.

Gomez, S. H., Tse, J., Wang, Y., Turner, B., Millner, A. J., Nock, M. K., & Dunn, E. C. (2017). Are there sensitive periods when child maltreatment substantially elevates suicide risk? Results from a nationally representative sample of adolescents. *Depression and Anxiety*, 34(8), 734-741. <https://doi.org/10.1002/da.22650>

Hantouche, E., Angst, J., & Azorin, J.-M. (2010). Explained factors of suicide attempts in major depression. *Journal of Affective Disorders*, 127(1), 305-308. <https://doi.org/10.1016/j.jad.2010.04.032>

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders : Preclinical and clinical studies. *Biological Psychiatry*, 49(12), 1023-1039.

Heim, Christine, Shugart, M., Craighead, W. E., & Nemeroff, C. B. (2010). Neurobiological and psychiatric consequences of child abuse and neglect. *Developmental Psychobiology*, 52(7), 671-690. <https://doi.org/10.1002/dev.20494>

Hooven, C., Nurius, P. S., Logan-Greene, P., & Thompson, E. A. (2012). Childhood Violence Exposure : Cumulative and Specific Effects on Adult Mental Health. *Journal of Family Violence*, 27(6), 511-522. <https://doi.org/10.1007/s10896-012-9438-0>

Hovens, J. G. F. M., Wiersma, J. E., Giltay, E. J., van Oppen, P., Spinhoven, P., Penninx, B. W. J. H., & Zitman, F. G. (2010). Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. Controls. *Acta Psychiatrica Scandinavica*, 122(1), 66-74. <https://doi.org/10.1111/j.1600-0447.2009.01491.x>

Janiri, D., De Rossi, P., Kotzalidis, G. D., Girardi, P., Koukopoulos, A. E., Reginaldi, D., Dotto, F., Manfredi, G., Jollant, F., Gorwood, P., Pompili, M., & Sani, G. (2018). Psychopathological characteristics and adverse childhood events are differentially associated with suicidal ideation and suicidal acts in mood disorders. *European Psychiatry: The Journal of the Association of European Psychiatrists*, 53, 31-36. <https://doi.org/10.1016/j.eurpsy.2018.05.009>

Liu, R. T., Alloy, L. B., Abramson, L. Y., Iacoviello, B. M., & Whitehouse, W. G. (2009). Emotional maltreatment and depression : Prospective prediction of depressive episodes. *Depression and Anxiety*, 26(2), 174-181. <https://doi.org/10.1002/da.20545>

Lutz, P.-E., Mechawar, N., & Turecki, G. (2017). Neuropathology of suicide : Recent findings and future directions. *Molecular Psychiatry*, 22(10), 1395-1412. <https://doi.org/10.1038/mp.2017.141>

Malhi, G. S., Parker, G. B., Crawford, J., Wilhelm, K., & Mitchell, P. B. (2005). Treatment-resistant depression : Resistant to definition? *Acta Psychiatrica Scandinavica*, 112(4), 302-309. <https://doi.org/10.1111/j.1600-0447.2005.00602.x>

Mann, J. J., Arango, V. A., Avenevoli, S., Brent, D. A., Champagne, F. A., Clayton, P., Currier, D., Dougherty, D. M., Haghghi, F., Hodge, S. E., Kleinman, J., Lehner, T., McMahon, F., Mościcki, E. K., Oquendo, M. A., Pandey, G. N., Pearson, J., Stanley, B., Terwilliger, J., & Wenzel, A. (2009). Candidate endophenotypes for genetic studies of suicidal behavior. *Biological Psychiatry*, 65(7), 556-563. <https://doi.org/10.1016/j.biopsych.2008.11.021>

McGirr, A., Renaud, J., Séguin, M., Alda, M., & Turecki, G. (2008). Course of major depressive disorder and suicide outcome : A psychological autopsy study. *The Journal of*

*Clinical Psychiatry*, 69(6), 966-970. <https://doi.org/10.4088/jcp.v69n0612>

McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonté, B., Szyf, M., Turecki, G., & Meaney, M. J. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience*, 12(3), 342-348. <https://doi.org/10.1038/nn.2270>

Miller, A. B., Esposito-Smythers, C., Weismore, J. T., & Renshaw, K. D. (2013). The relation between child maltreatment and adolescent suicidal behavior : A systematic review and critical examination of the literature. *Clinical Child and Family Psychology Review*, 16(2), 146-172. <https://doi.org/10.1007/s10567-013-0131-5>

Miller, A. H. (2009). Norman Cousins Lecture. Mechanisms of cytokine-induced behavioral changes : Psychoneuroimmunology at the translational interface. *Brain, Behavior, and Immunity*, 23(2), 149-158. <https://doi.org/10.1016/j.bbi.2008.08.006>

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents : The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry*, 65(9), 732-741. <https://doi.org/10.1016/j.biopsych.2008.11.029>

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression : From evolutionary imperative to modern treatment target. *Nature Reviews. Immunology*, 16(1), 22-34. <https://doi.org/10.1038/nri.2015.5>

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry: The Journal of Mental Science*, 134, 382-389.

Nanni, V., Uher, R., & Danese, A. (2012). Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression : A Meta-Analysis. *American Journal of Psychiatry*, 169(2), 141-151. <https://doi.org/10.1176/appi.ajp.2011.11020335>

Nelsen, M. R., & Dunner, D. L. (1995). Clinical and differential diagnostic aspects of treatment-resistant depression. *Journal of Psychiatric Research*, 29(1), 43-50.

Nock, M. K., Borges, G., Bromet, E. J., Alonso, J., Angermeyer, M., Beautrais, A., Bruffaerts, R., Chiu, W. T., de Girolamo, G., Gluzman, S., de Graaf, R., Gureje, O., Haro, J. M., Huang, Y., Karam, E., Kessler, R. C., Lepine, J. P., Levinson, D., Medina-Mora, M. E., ... Williams, D. (2008). Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *The British Journal of Psychiatry: The Journal of Mental Science*, 192(2), 98-105. <https://doi.org/10.1192/bjp.bp.107.040113>

Nock, M. K., Green, J. G., Hwang, I., McLaughlin, K. A., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2013). Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents : Results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry*, 70(3), 300-310. <https://doi.org/10.1001/2013.jamapsychiatry.55>

Nock, M. K., Hwang, I., Sampson, N., Kessler, R. C., Angermeyer, M., Beautrais, A., Borges, G., Bromet, E., Bruffaerts, R., de Girolamo, G., de Graaf, R., Florescu, S., Gureje, O., Haro, J. M., Hu, C., Huang, Y., Karam, E. G., Kawakami, N., Kovess, V., ... Williams, D. R. (2009). Cross-national analysis of the associations among mental disorders and suicidal behavior : Findings from the WHO World Mental Health Surveys. *PLoS Medicine*, 6(8), e1000123. <https://doi.org/10.1371/journal.pmed.1000123>

Norman, R. E., Byambaa, M., De, R., Butchart, A., Scott, J., & Vos, T. (2012). The long-term health consequences of child physical abuse, emotional abuse, and neglect : A systematic review and meta-analysis. *PLoS Medicine*, 9(11), e1001349. <https://doi.org/10.1371/journal.pmed.1001349>

Ozcan, S., Gica, S., & Gulec, H. (2020). Suicidal behavior in treatment resistant major depressive disorder patients treated with transcranial magnetic stimulation(TMS) and its relationship with cognitive functions. *Psychiatry Research*, 286, 112873. <https://doi.org/10.1016/j.psychres.2020.112873>

- Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology, 51*(6), 768-774.
- Plaisant, O., Courtois, R., Réveillère, C., Mendelsohn, G. A., & John, O. P. (2010). Validation par analyse factorielle du Big Five Inventory français (BFI-Fr). Analyse convergente avec le NEO-PI-R. *Annales Médico-psychologiques, revue psychiatrique, 168*(2), 97-106. <https://doi.org/10.1016/j.amp.2009.09.003>
- Ponsoni, A., Branco, L. D., Cotrena, C., Shansis, F. M., Grassi-Oliveira, R., & Fonseca, R. P. (2018). Self-reported inhibition predicts history of suicide attempts in bipolar disorder and major depression. *Comprehensive Psychiatry, 82*, 89-94. <https://doi.org/10.1016/j.comppsy.2018.01.011>
- Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., Currier, G. W., Melvin, G. A., Greenhill, L., Shen, S., & Mann, J. J. (2011). The Columbia-Suicide Severity Rating Scale : Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *The American Journal of Psychiatry, 168*(12), 1266-1277. <https://doi.org/10.1176/appi.ajp.2011.10111704>
- R Core Team. (2019). *R: A Language and environment for statistical computing. (Version 3.6) [Computer software]. Retrieved from <https://cran.r-project.org/>.*
- Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues : Inflammation and the pathogenesis of depression. *Trends in Immunology, 27*(1), 24-31. <https://doi.org/10.1016/j.it.2005.11.006>
- Rosseel, Y. (2012). *Lavaan : An R Package for Structural Equation Modeling. , 48*(2), 1-36. *Link. 48*(2), 1-36.
- Sackeim, H. A. (2001). The definition and meaning of treatment-resistant depression. *The Journal of Clinical Psychiatry, 62 Suppl 16*, 10-17.
- Sit, D., Luther, J., Buysse, D., Dills, J. L., Eng, H., Okun, M., Wisniewski, S., & Wisner, K. L. (2015). Suicidal ideation in depressed postpartum women : Associations with childhood trauma, sleep disturbance and anxiety. *Journal of Psychiatric Research, 66-67*, 95-104. <https://doi.org/10.1016/j.jpsychires.2015.04.021>
- Thase, M. E., & Rush, A. J. (1997). When at first you don't succeed : Sequential strategies for antidepressant nonresponders. *The Journal of Clinical Psychiatry, 58 Suppl 13*, 23-29.
- The jamovi project. (2020). *jamovi (Version 1.2) [Computer Software]. Retrieved from <https://www.jamovi.org>.*
- Tunnard, C., Rane, L. J., Wooderson, S. C., Markopoulou, K., Poon, L., Fekadu, A., Juruena, M., & Cleare, A. J. (2014). The impact of childhood adversity on suicidality and clinical course in treatment-resistant depression. *Journal of Affective Disorders, 152-154*, 122-130. <https://doi.org/10.1016/j.jad.2013.06.037>
- Turecki, G., & Brent, D. A. (2016). Suicide and suicidal behaviour. *Lancet (London, England), 387*(10024), 1227-1239. [https://doi.org/10.1016/S0140-6736\(15\)00234-2](https://doi.org/10.1016/S0140-6736(15)00234-2)
- Turecki, G., Brent, D. A., Gunnell, D., O'Connor, R. C., Oquendo, M. A., Pirakis, J., & Stanley, B. H. (2019). Suicide and suicide risk. *Nature Reviews. Disease Primers, 5*(1), 74. <https://doi.org/10.1038/s41572-019-0121-0>
- Turecki, G., & Meaney, M. J. (2016). Effects of the Social Environment and Stress on Glucocorticoid Receptor Gene Methylation : A Systematic Review. *Biological Psychiatry, 79*(2), 87-96. <https://doi.org/10.1016/j.biopsych.2014.11.022>
- Wainwright, N. W. J., & Surtees, P. G. (2002). Childhood adversity, gender and depression over the life-course. *Journal of Affective Disorders, 72*(1), 33-44.
- WHO. (2014). *Mental health : Suicide prevention. 2014. [Http://www.who.int/mental\\_health/suicide-prevention/en/](http://www.who.int/mental_health/suicide-prevention/en/).*
- Wiersma, J. E., Hovens, J. G. F. M., van Oppen, P., Giltay, E. J., van Schaik, D. J. F., Beekman, A. T. F., & Penninx, B. W. J. H. (2009). The importance of childhood trauma and



childhood life events for chronicity of depression in adults. *The Journal of Clinical Psychiatry*, 70(7), 983-989.

Yrondi, A., Aouizerate, B., Bennabi, D., Richieri, R., D'Amato, T., Bellivier, F., Bougerol, T., Horn, M., Camus, V., Courtet, P., Doumy, O., Genty, J. B., Holtzmann, J., Lançon, C., Leboyer, M., Llorca, P. M., Maruani, J., Moirand, R., Molière, F., ... El-Hage, W. (2020). Childhood maltreatment and clinical severity of treatment-resistant depression in a French cohort of outpatients (FACE-DR) : One-year follow-up. *Depression and Anxiety*, 37(4), 365-374. <https://doi.org/10.1002/da.22997>

Yrondi, A., Bennabi, D., Haffen, E., Garnier, M., Bellivier, F., Bourgerol, T., Camus, V., D'Amato, T., Doumy, O., Haesebaert, F., Holtzmann, J., Lançon, C., Vignaud, P., Moliere, F., Nieto, I., Richieri, R. M., Domenech, P., Rabu, C., Mallet, L., ... Aouizerate, B. (2017). Significant Need for a French Network of Expert Centers Enabling a Better Characterization and Management of Treatment-Resistant Depression (Fondation FondaMental). *Frontiers in Psychiatry*, 8, 244. <https://doi.org/10.3389/fpsy.2017.00244>

Ystgaard, M., Hestetun, I., Loeb, M., & Mehlum, L. (2004). Is there a specific relationship between childhood sexual and physical abuse and repeated suicidal behavior? *Child Abuse & Neglect*, 28(8), 863-875. <https://doi.org/10.1016/j.chiabu.2004.01.009>

Zhang, M., Han, J., Shi, J., Ding, H., Wang, K., Kang, C., & Gong, J. (2018). Personality traits as possible mediators in the relationship between childhood trauma and depressive symptoms in Chinese adolescents. *Journal of Psychiatric Research*, 103, 150-155. <https://doi.org/10.1016/j.jpsychires.2018.05.019>

### **Tables**

**Table 1.** Population characteristics.

**Table 2.** Comparison between patients filling CTQ and non-filling CT

**Table 3.** Results of general linear model with mediation model (CTQ)

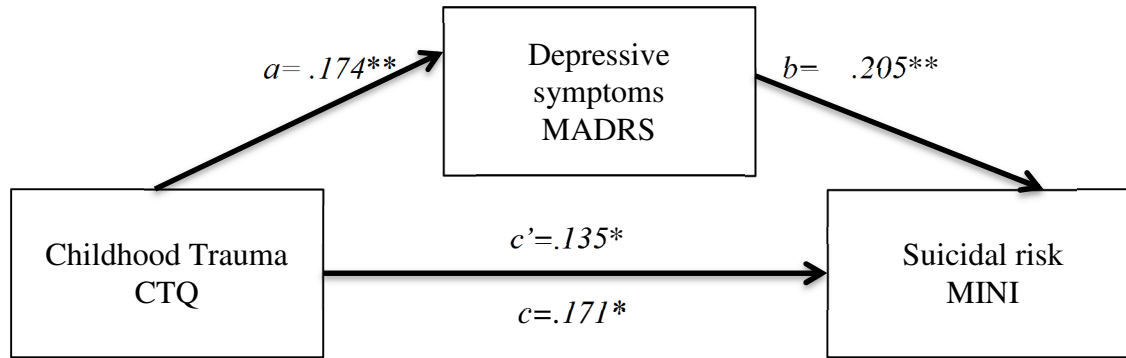
**Table 4.** Results of general linear model with mediation model (sub-type of childhood trauma)

### **Figures**

**Figure 1 :** Depressive symptoms as mediator of childhood trauma on suicidal risk

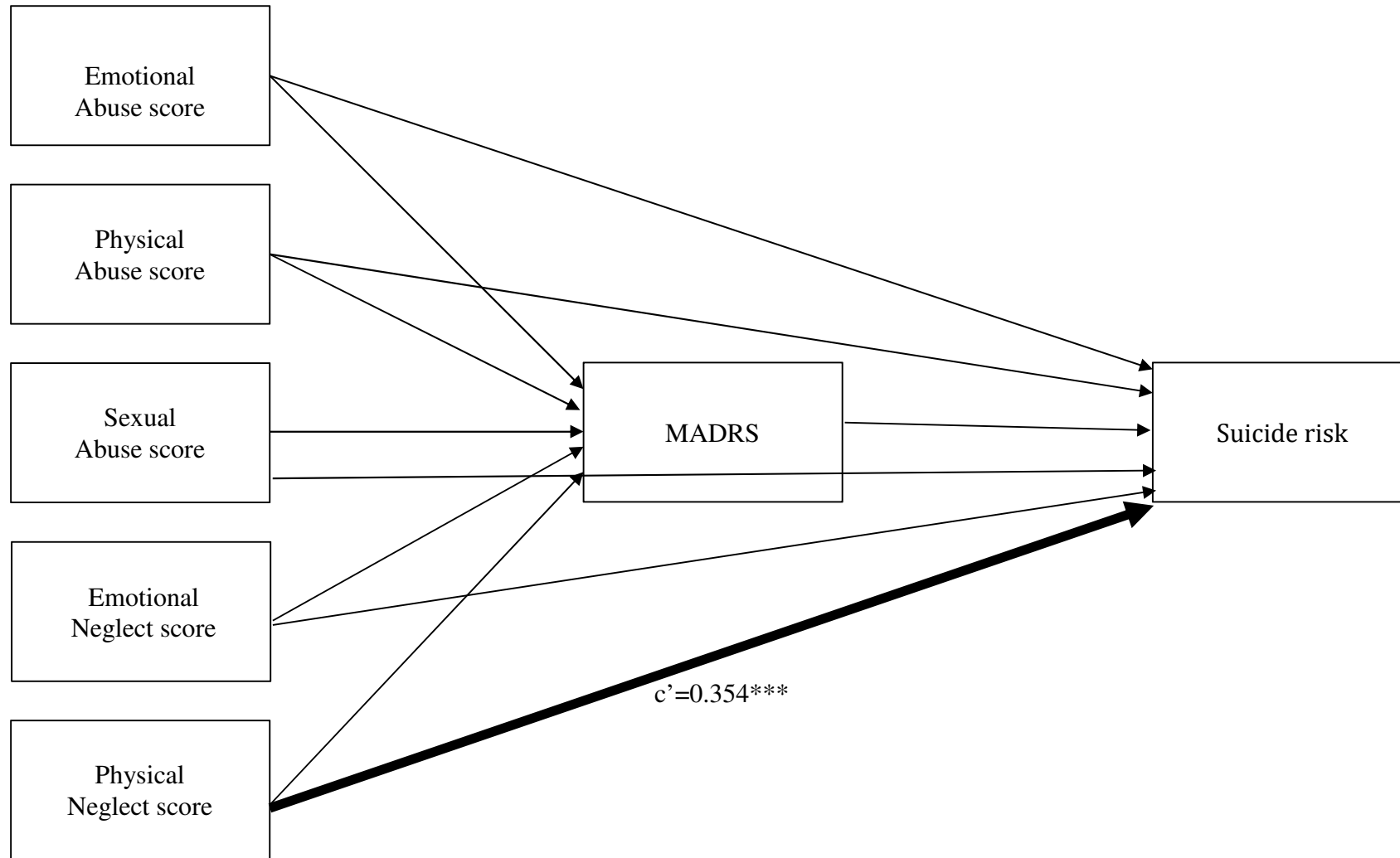
**Figure 2 :** Association between childhood trauma subtype and suicidal risk

**Figure 1** : Depressive symptoms as mediator of childhood trauma on suicidal risk



*MADRS : Montgomery and Asberg Depression Rating Scale ; CTQ : Childhood Trauma Questionnaire ;  $ab$  : indirect effect ;  $c'$  : direct effect ;  $c$  : total effect \* :  $p < .05$ , \*\* $p < = .01$ , ns : non significant*

**Figure 2 :** Association between childhood trauma subtype and suicidal risk



*MADRS : Montgomery and Asberg Depression Rating Scale, arrow in bold: association statistically significant; c' = direct effect; \*\*\* = <0.001*

**Table 1.** Population characteristics.

	<b>N</b>	<b>Mean (SD)</b>
Age, years	291	53.21 (12.93)
Females, %	181 (62.2%)	
ATHF	239	4.03 (.51)
CTQ, total score	256	42.57 (14.51)
Emotional abuse, score	256	6.46 (2.88)
None (5-8)	216 (84.4%)	
Low (9-12)	28 (10.9%)	
Moderate (13-15)	5 (2%)	
Severe (16+)	7 (2.7%)	
Physical abuse, score	256	12.77 (5.06)
None (5-7)	40 (15.6%)	
Low (8-9)	42 (16.4%)	
Moderate (10-12)	51 (19.9%)	
Severe (13+)	123 (48.8%)	
Sexual abuse, score	256	7.42 (2.72)
None (5)	84 (32.8%)	
Low (6-7)	69 (27%)	
Moderate (8-12)	86 (33.6%)	
Severe (13+)	17 (6.6%)	
Emotional neglect, score	256	6.27 (3.46)
None (5-9)	230 (89.8%)	
Low (10-14)	12 (4.7%)	
Moderate (15-17)	7 (2.7%)	
Severe (18+)	7 (2.7%)	
Physical neglect, score	256	9.66 (5.07)
None (5-7)	121 (47.3%)	
Low (8-9)	32 (12.5%)	
Moderate (10-12)	37 (14.5%)	
Severe (13+)	66 (25.8%)	

BFI extraversion	252	2.26 (.83)
BFI agreeableness	252	4.11 (.48)
BFI neuroticism	231	3.94 (.62)
BFI conscientiousness	231	3.46 (.76)
BFI openness	252	2.85 (.81)
BIS	247	64.26 (9.6)
MADRS	282	28.92 (6.90)
CSSRS	202	12.91 (7.63)
MINI suicide score	244	8.85 (10.4)

*ATHF: Antidepressant Treatment History Form; BFI: Big Five Inventory; BIS: Barratt Impulsivity Scale; CSSRS: Columbia Severity Suicide Rating Scale; CTQ: Child Trauma Questionnaire; MADRS: Montgomery-Åsberg Depression Rating Scale; MINI: Mini International Neuropsychiatric Interview; N: Number; SD: Standard Deviation.*

**Table 2.** Comparison between patients filling CTQ and non-filling CTQ

Variables	group	N	Mean (SD)	p
Age	CTQ	256	52.73 (12.95)	0.085 <sup>t</sup>
	No CTQ	35		
Sex (F)	CTQ	158		0.648 <sup>c</sup>
	No CTQ	23		
MADRS	CTQ	253	28.99 (6.73)	0.617 <sup>t</sup>
	No CTQ	29	28.31 (8.35)	
MINI suicide risk	CTQ	217	9.02 (10.62)	0.458 <sup>t</sup>
	No CTQ	27	7.44(8.47)	
CSSRS	CTQ	181	16 (9.03)	0.303 <sup>t</sup>
	No CTQ	21	14 (8.31)	

<sup>c</sup> : Chi2 ; CSSRS : Columbia Suicide Severity Rating Scale suicidal ideation score; CTQ : Childhood Trauma Questionnaire score ; MADRS : Montgomery Asberg Depression Rating Scale ;MINI : Mini International Neuropsychiatric Interview ; p : p-value, SD : Standard Deviation ; <sup>t</sup> : t-test

**Table 3.** Results of general linear model with mediation model (CTQ)

Interactions	95% C.I.
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Type	Effect	Lower	Upper	$\beta$	p
Indirect	CTQ $\Rightarrow$ MADRS $\Rightarrow$ MINI suicide score	2.6e-4	0.052	0.036	0.048
Component	CTQ $\Rightarrow$ MADRS	0.019	0.137	0.174	0.010
	MADRS $\Rightarrow$ MINI suicide score	0.12	0.546	0.205	0.002
Direct	CTQ $\Rightarrow$ MINI suicide score	0.003	0.194	0.135	0.043
Total	CTQ $\Rightarrow$ MINI suicide score	0.028	0.22	0.171	0.011

$\beta$ :  $\beta$  value ; CI : confident Interval ; CTQ : Childhood Trauma Questionnaire score ; MADRS : Montgomery Asberg Depression Rating Scale ; MINI : Mini International Neuropsychiatric Interview ; p : p-value

**Table 4.** Results of general linear model with mediation model (sub-type of childhood trauma)

Interactions					
Type	Effect	95% C.I.		$\beta$	p
		Lower	Upper		
Indirect	Emotional Abuse $\Rightarrow$ MADRS $\Rightarrow$ MINI suicide score	-0.156	0.161	7.1e-4	0.975
	Physical Abuse $\Rightarrow$ MADRS $\Rightarrow$ MINI suicide score	0.002	0.226	0.055	0.047
	Sexual Abuse $\Rightarrow$ MADRS $\Rightarrow$ MINI suicide score	0.008	0.382	0.050	0.041
	Emotional Neglect $\Rightarrow$ MADRS $\Rightarrow$ MINI suicide score	-0.072	0.171	0.016	0.428
	Physical Neglect $\Rightarrow$ MADRS M0 $\Rightarrow$ MINI suicide score	-0.228	0.004	-0.053	0.059
Component	Emotional Abuse $\Rightarrow$ MADRS	-0.377	0.389	0.003	0.975
	MADRS $\Rightarrow$ MINI suicide score	0.2	0.627	0.255	< .001

Interactions					
Type	Effect	95% C.I.		$\beta$	p
		Lower	Upper		
Direct	Physical Abuse $\Rightarrow$ MADRS	0.044	0.505	0.215	0.020
	Sexual Abuse $\Rightarrow$ MADRS	0.091	0.853	0.198	0.015
	Emotional Neglect $\Rightarrow$ MADRS	-0.169	0.405	0.062	0.418
	Physical Neglect $\Rightarrow$ MADRS	-0.515	-0.027	-0.208	0.029
	Emotional Abuse $\Rightarrow$ MINI suicide score	-0.838	0.386	-0.064	0.469
	Physical Abuse $\Rightarrow$ MINI suicide score	-0.611	0.134	-0.115	0.210
	Sexual Abuse $\Rightarrow$ MINI suicide score	-0.823	0.409	-0.053	0.511
	Emotional Neglect $\Rightarrow$ MINI suicide score	-0.428	0.489	0.01	0.896
	Physical Neglect $\Rightarrow$ MINI suicide score	0.354	1.141	0.354	< .001
	Total	Emotional Abuse $\Rightarrow$ MINI suicide score	-0.857	0.410	-0.063
Physical Abuse $\Rightarrow$ MINI suicide score		-0.506	0.257	-0.060	0.522
Sexual Abuse $\Rightarrow$ MINI suicide score		-0.641	0.617	-0.003	0.971
Emotional Neglect $\Rightarrow$ MINI suicide score		-0.395	0.554	0.025	0.742
Physical Neglect $\Rightarrow$ MINI suicide score		0.232	1.038	0.301	0.002

$\beta$ :  $\beta$  value ; CI : confident Interval ; CTQ : Childhood Trauma Questionnaire score ; MADRS : Montgomery Asberg Depression Rating Scale ; MINI : Mini International Neuropsychiatric Interview ; p : p-value