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Review article

Association between adverse childhood experiences and suicidal behavior in schizophrenia spectrum disorders: A systematic review and meta-analysis

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ABSTRACT

Assessing and managing suicide behaviors is highly relevant to individuals with schizophrenia spectrum disorders. Our study aims to assess the association between adverse childhood experiences and suicidal behaviors in individuals with schizophrenia spectrum disorders.

We included observational studies comparing the probability of suicide behaviors in adults with schizophrenia spectrum disorders exposed and unexposed to adverse childhood experiences. Odds ratio estimates were obtained by pooling data using a random-effects pairwise meta-analysis. Standardized criteria were used to assess the strength of the association of the pooled estimate. We found 21 eligible studies reporting outcomes for 6257 individuals from 11 countries. The primary outcome revealed an association between any suicidal behavior and adverse childhood experiences, which resulted "highly suggestive" according to validated Umbrella Criteria. Similarly, a positive association was confirmed for suicidal ideation and suicide attempt and for any subtype of adverse childhood experience. This meta-analysis showed that exposure to adverse childhood experiences strongly increases the probability of suicide behaviors in people with schizophrenia spectrum disorders.

1. Introduction

Schizophrenia spectrum disorders (SSDs) have a lifetime prevalence rate of about 7 out of 1000 individuals, (McGrath et al., 2008) and are frequently associated with long-term poor social and functional outcomes (Peritogiannis et al., 2020). Individuals with SSDs have an average life expectancy of about 15 years shorter compared to the general population, (Hjorthøj et al., 2017) which is attributable to multiple causes, including medical comorbidities and death by suicide (Correll et al., 2022). It has been estimated that about 20% of individuals with schizophrenia and about half of those with schizoaffective disorders attempt suicide at least once during their life, (Álvarez et al., 2022), and about one-third perpetrate episodes of non-suicidal self-injury (Correll et al., 2022).

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A variety of risk factors might increase the probability of suicide behaviors in the general population (Favril et al., 2022). As for individuals with SSD, large reviews and meta-analyses, (Correll et al., 2022; Hor and Taylor, 2010) pointed out comorbid depressive disorders, active positive symptoms, personal and family history of suicide attempts, substance misuse, agitation or restlessness, recent loss, and poor treatment adherence as prominent risk factors. Notably, these reviews did not consider early traumatic experiences in their analyses. In recent years, however, the role of adverse childhood experiences (ACEs) as a potential role for suicide behaviors has attracted increasing attention in this population group (Sahle et al., 2022). Disentangling the risk for different types of trauma, such as sexual abuse, neglect, bullying, and physical and verbal abuse (Kalmakis and Chandler, 2014), is particularly difficult considering that a history of ACEs commonly includes multiple traumatic experiences (70% of traumatized children suffered on average three different types of trauma), (Cloitre et al., 2009) which are commonly interlaced to each other. ACEs have been associated with neurodevelopment abnormalities, including decreased gray matter in the prefrontal cortex and abnormal functional connection, (Cancel et al., 2019) and are largely recognized as a trans-diagnostic risk factor in mental health, associated with the risk of developing chronic psychoses (Arango et al., 2021; Varese et al., 2012). It has been estimated that ACEs occurred in about one-third of individuals with SSD (Bonoldi et al., 2013) and are associated with a severer course of disease and possible refractoriness to treatments (McKay et al., 2021).

The association between ACEs and suicide behaviors in individuals with SSD has been repeatedly hypothesized but contrasting results have emerged from available studies (Alli et al., 2019; Berardelli et al., 2021; Hor and Taylor, 2010; Roy, 2005). Further, the possible association between ACEs and non-suicidal self-injury in people with SSD has been seldom discussed in the existing literature (Güney et al., 2020). So far, a comprehensive literature synthesis has never been conducted on this important topic. On these grounds, we carried out a systematic review and meta-analysis to quantify and characterize the probability of suicide behavior in individuals with SSD who experienced different types of ACEs.

2. Methods

The protocol of this systematic review was publicly registered in advance in PROSPERO (International Prospective Register of Systematic Review) (CRD42022351147).

2.1. Eligibility criteria

Studies were included if they were observational prospective or retrospective cohort, case-control or cross-sectional studies reporting data on suicide behavior and/or non-suicidal self-injury in individuals with SSD (according to the DSM or ICD) exposed to ACEs compared to unexposed individuals. We included studies with individuals of 16 years or older, of either sex and of any ethnicity. Studies with "mixed" clinical populations were included only if the proportion of individuals with diagnoses other than SSD (e.g., affective disorders) was 20% or less. We considered ACEs as traumatic experiences occurring during childhood, including various forms of abuse, neglect, bullying, physical and verbal violence, and sexual abuse, (Kalmakis and Chandler, 2014) as reported by authors in each primary study through clinical interviews, or as assessed with validated rating scales. Suicide behaviors were classified as suicidal ideation, suicide attempt, and suicide death.

2.2. Outcomes

The primary outcome was the probability of any suicide behavior (including suicidal ideation, suicide attempt, and suicide death) in individuals suffering from SSD and exposed to any ACE, compared with unexposed individuals. Secondary outcomes included: (i) probability of suicide behavior as a function of the Child Trauma Questionnaire Short Form (CTQ-SF) score; (Bernstein et al., 2003) which we obtained by pooling the most adjusted ORs from logistic regressions exploring this risk, as reported by each study; (ii) suicidal ideation in individuals exposed to any ACE; (iii) suicide attempt in individuals exposed to any ACE; (iv) suicide death in individuals exposed to any ACE; (v) non-suicidal self-injury in individuals exposed to any ACE; (vi) any suicide behavior in individuals exposed to physical abuse; (vii) any suicide behavior in individuals exposed to physical neglect; (viii) any suicide behavior in individuals exposed to sexual abuse; (ix) any suicide behavior in individuals exposed to emotional abuse; (x) any suicide behavior in individuals exposed to emotional neglect.

For the primary outcome, we performed the following sensitivity analyses: (i) only studies recruiting individuals with a diagnosis of schizophrenia; (ii) excluding data imputed from a continuous measure (i.e., rating scale score); (iii) only studies with low risk of bias (defined as a total score of 8–9 at Newcastle-Ottawa Scale) (Wells et al., 2008).

Further, we aimed to perform meta-regression analyses for the following variables indicated in the meta-analysis by Favril and colleagues, (Favril et al., 2022) provided that at least 10 studies contributed: age, sex, marital status, having children, level of education, socioeconomic status, country income, being religious, physical illness, mental illness duration, age of onset, duration of untreated psychosis, tobacco smoking, alcohol, and substance abuse, family history of suicide behavior, any comorbid mental disorders, depression, personality disorder.

2.3. Search strategy and study selection

We selected eligible studies following the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting standards (PRISMA). A literature search was carried out through the electronic databases PubMed, PsycINFO, Web of Science, and CINHAL, from inception to May 31st, 2023, with no language restrictions (see eAppendix, Supplement 2 for the full search strategy). After excluding duplicates, two researchers (among VB, RDS, and LVR) independently screened titles, abstracts, and, subsequently, full texts of identified records. In case of disagreements on inclusion or exclusion, a consensus was reached by involving a senior researcher (GO, CB).

2.4. Data extraction and synthesis

Statistical analyses were designed, performed, and reported following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000). We extracted from each study the number of individuals with and without the event of interest (i.e., suicide behavior) in the group of those exposed and unexposed to ACEs, and we calculated summary odds ratios (ORs) and 95% confidence intervals (CIs). When available, we extracted ORs adjusted for sociodemographic and clinical characteristics from primary studies. If the number of individuals exposed and unexposed was not available, we imputed it from mean scores and standard deviations of rating scales assessing ACEs, using cut-off scores indicating clinically relevant traumatic events, according to a validated methodology (Furukawa et al., 2006). Data were pooled and an overall estimate of ORs was obtained using the *DerSimonian and Laird* random-effects model, taking into account between study variability (DerSimonian and Laird, 1986). We used the I-squared statistics (I^2) and visual inspection of forest plots to investigate statistical heterogeneity. Unrestricted maximum likelihood random-effects meta-regression was employed to find whether sociodemographic and clinical variables mediated the association between ACEs exposure and suicide behaviors in individuals with SSD.

Included studies were assessed with the Newcastle-Ottawa Scale (NOS), which evaluates the risk of bias of observational studies on three domains (selection, comparability, and exposure) and provides an overall score ranging from 1 (highest risk of bias) to 9 (lowest risk of

bias) (Wells et al., 2008). Two researchers (RDS, LVR) assessed the risk independently, and disagreements were discussed with a third researcher (VB, GO). Moreover, for the primary outcome, we assessed the overall strength of association according to the Umbrella Review Criteria, (Ioannidis, 2009) taking into account the following elements: (a) the number of cases (i.e., events) included in the analysis; (b) the magnitude of the p-value of the random-effect meta-analysis; (c) small study effects (an indicator of publication bias); (d) excess of significance bias; (e) predictive intervals; (f) nominal statistical significance of the largest study included; (g) between-study heterogeneity. According to this assessment, we classified the association as "Convincing" (Class I), "Highly Suggestive" (Class II), "Suggestive" (Class III), or "Weak" (Class IV).

All statistical analyses were carried out using Stata version 17 and Review Manager version 5.4.

3. Results

3.1. Characteristics of included studies

The electronic and manual literature search yielded 3412 records, 2259 of which underwent title/abstract screening after removing duplicates. After this process, 136 full texts were assessed for eligibility, with 21 studies (including 6257 subjects) (Aas et al., 2023; Alli et al., 2019; Alvarez et al., 2011; Bani-Fatemi et al., 2019; Chalker et al., 2022; Cui et al., 2019; Hassan et al., 2016; Hettige et al., 2017; Hui and Hilton, 2022; Hwang et al., 2020; Karanović et al., 2017; Koola et al., 2018; Mohammadzadeh et al., 2019; Neider et al., 2016; Prokopez et al., 2020; Rosenberg et al., 2007; Roy, 2005; Shah et al., 2014; Togay et al., 2015; Tousignant et al., 2011; Zhang et al., 2021) meeting inclusion criteria and contributing to at least one meta-analysis (Fig. 1 and eAppendix, Supplements 2 and 3). Table 1 summarizes the characteristics of included studies. Cohort and cross-sectional studies generally recruited individuals with no current suicide behaviors and collected data on ACEs and suicide behaviors retrospectively, through clinical interviews and rating scales (i.e., the CTQ-SF in most cases), while case-control studies recruited individuals based on current suicide behaviors and compared them with controls, collecting only ACEs retrospectively. For six studies, (Aas et al., 2023; Hui and Hilton, 2022; Karanović et al., 2017; Koola et al., 2018; Shah et al., 2014; Togay et al., 2015) we were able to obtain unpublished data from the original authors. For seven studies, (Bani-Fatemi et al., 2019; Hettige et al., 2017; Hwang et al., 2020; Karanović et al., 2017; Mohammadzadeh et al., 2019; Roy, 2005; Togay et al., 2015) missing data were imputed using continuous measures, mainly CTQ-SF mean score and its standard deviation (SD). The mean sample size of included studies was 298 individuals (median 135, inter-quartile range (IQR) 88–345); the mean age of participants was 41.0 years (SD 6.51; median 42.0; IQR 38.4–43.9); the mean proportion of women was 42.6% (SD 16.33; median 45.5%; IQR 33–57%). Thirteen out of 21 studies showed an overall low risk of bias according to the NOS (total score 8–9), while, for the remaining studies, the risk of bias was moderate (total score 4–7) (see eAppendix, Supplement 4). All imputed data are thoroughly reported in the eAppendix (Supplement 5).

3.2. Association between ACEs and suicide behavior

Meta-analysis of the primary outcome revealed an association between exposure to ACEs and suicide behavior (OR 1.92; 95% CI 1.51 to

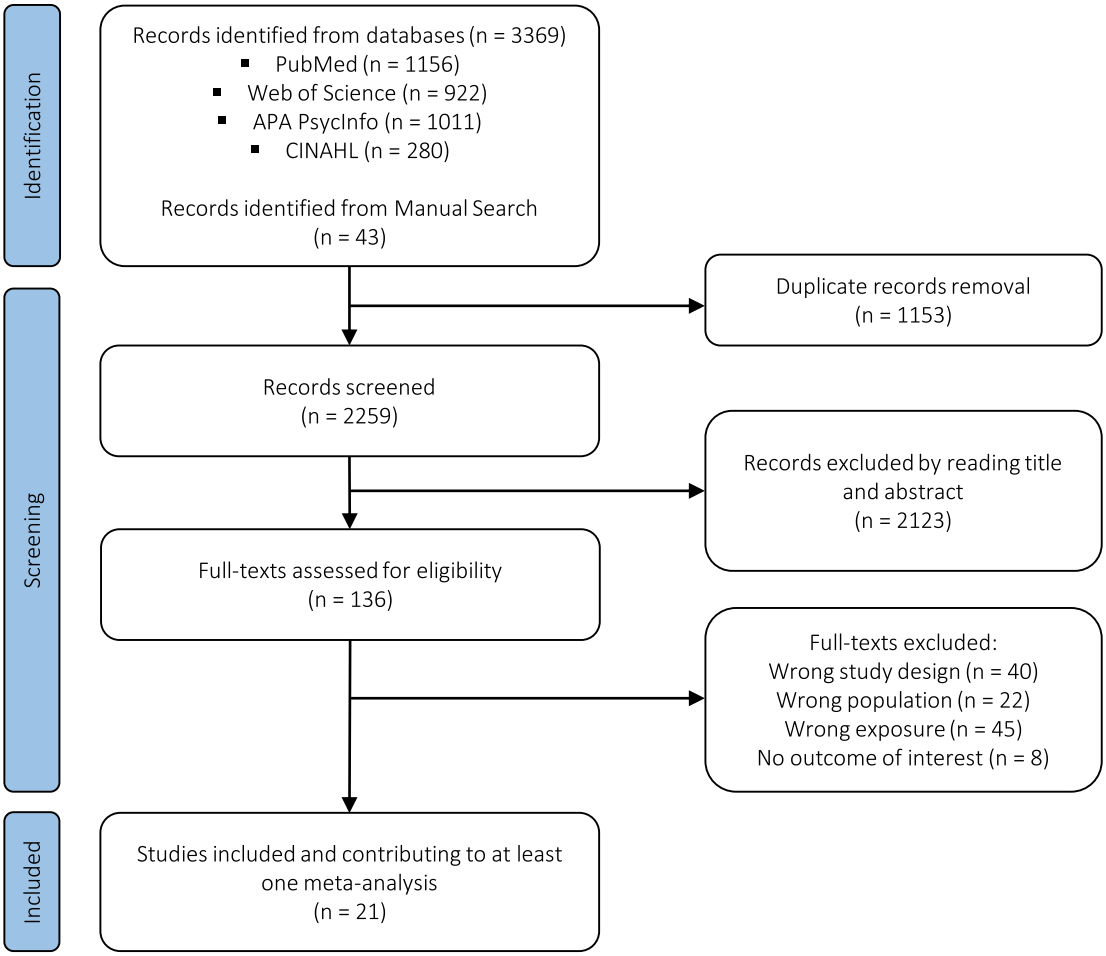

Fig. 1. Flow-chart describing the study selection process.

Table 1
Characteristics of included studies. "Included diagnosis" and "overall sample" report only the population of interest for this meta-analysis.

First author, year	Country	Diagnoses in the SSD (criteria)	Mean age ± SD	% women	Overall sample	N. events (any suicide behavior)	Study design	Types of ACEs	Type of suicide behavior	NOS overall score
Aas 2022 [46]	Norway	SCZ (DSM-IV)	30.3 ± 8.6	38.6%	348	93	Cohort	NS	SA	9
Alli 2019 [26]	Canada	SCZ 55.1%; SCZ-AFF 36.7%; other SSD 8.2% (DSM-IV)	46.6 ± 11.8	32.6%	52	16	Case-control	SexA, PA, PN, EA, EN	SA, SI	5
Alvarez 2011 [47]	Spain	SCZ (DSM-IV)	39.4 ± 10.4	47.1%	52	24	Cohort	SexA, PA, EA	SA	8
Bani-Fatemi 2019 [48]	Canada	SCZ or SCZ-AFF (DSM-IV)	44.7 ± 13.1	30.8%	224	93	Case-control	SA, SI	SA, SI	9
Chalker 2022 [49]	USA	SCZ 47.4%; SCZ-AFF 52.6% (DSM-5)	43.9 + 11.2	55.2%	96	81	Cross-sectional	EA, EN, PA, PN, SexA	SA, SI	7
Cui 2019 [50]	China	SCZ (DSM-5)	27.5 ± 7.2	57.0%	314	154	Cohort	SexA, PA, EA	SI	8
Hassan 2016 [51]	Canada	SCZ or SCZ-AFF (DSM-IV)	42.9 ± 12.8	26.6%	361	141	Cohort	SexA, PA, PN, EA, EN	SA	9
Hettige 2017 [52]	Canada	SSD (DSM-IV)	41.0 ± 13.1	30.1%	345	131	Case-control	SexA, PA, PN, EA, EN	SA	9
Hui 2022 [53]	Canada	SSD (forensic setting) (DSM-IV)	35.2 ± 12.3	0%	206	84	Cross-sectional	SexA, PA, EA, EN	SA	9
Hwang 2020 [54]	Canada	SCZ (DSM-5)	40.9 ± 13.4	36.0%	182	44	Cross-sectional	NS	SI	9
Karanovic 2017 [55]	Serbia	SCZ (DSM-IV)	42.0 ± 11.6	64.9%	135	50	Cohort	SexA, PA, EA	SA	9
Koola 2018 [56]	USA	SCZ (NS)	55.3 ± 12.6	22.8%	942	90	Cohort	SexA, PA	SA	8
Mohammadzadeh 2019 [57]	Iran	SCZ (DSM-IV-TR)	34.8 ± 9.1	58.5%	82	34	Case-control	SexA, PA, EA, EN, PN	SA	7
Neider 2016 [58]	Sweden	SCZ 91.9%; SCZ-AFF 7.1%; other SSD 1%	Median: 27 (range 18–48)	34.3%	88	11	Cohort	Bullying	SD	6
Prokopez 2020 [59]	Argentina	SCZ (DSM-IV/ICD-10)	44.5 ± 12.9	50.0%	100	49	Cross-sectional	SexA, PA, EA, EN, PN	SI	5
Rosenberg 2007 [60]	USA	SCZ 70%; SCZ-AFF 30% (DSM-IV)	42.0 ± 9.0	32.2%	569	492	Cohort	SexA, PA	SA, SI	5
Roy 2005 [25]	USA	SCZ (DSM-IV)	41.4 ± 9.5	27.0%	100	50	Case-control	SexA, PA, EA, EN, PN	SA	6
Shah 2014 [61]	Australia	SSD (ICD-10)	38.4 ± 11.2	40.4%	1825	558	Cross-sectional	NS	SA, SI	9
Togay 2015 [62]	Turkey	SCZ (DSM-IV)	NA	58.0%	92	17	Cohort	SexA, PA, EA, EN, PN	SA	4
Tousignant 2011 [63]	Canada	SCZ 89.2%; SCZ-AFF 12.3%; other SSD 1.5% (DSM-IV)	33.3 ± 10.0	23.9%	65	32	Case-control	NS	SA	8
Zhang 2021 [64]	China	SCZ (DSM-IV)	39.7 ± 9.7	45.8%	83	33	Case-control	SexA, PA, EA, EN, PN	SI	9

SD=Suicide death; DSM=Diagnostic and Statistical Manual of Mental Disorders; EA=Emotional abuse; EN=Emotional neglect; ICD=International Classification of Diseases; NOS=Newcastle-Ottawa Scale; NS=Not Specified; PA=Physical abuse; PN=Physical neglect; SA=Suicide Attempt; SD=Standard Deviation; SexA=Sexual abuse; SI=Suicidal Ideation; SCZ=Schizophrenia; SSD=Schizophrenia Spectrum Disorder.

2.45) (Fig. 2). According to the Umbrella Review Criteria, the strength of association was "Highly Suggestive" (Class II). The following shortcomings limited the strength of the association: moderate heterogeneity (I^2=59%); risk of small-study effects according to Egger's test (p = 0.008); the presence of an excess of significance bias ($p<0.001$); and predictive intervals including the null value (0.84 to 4.42) (see eAppendix, Supplement 6). Sensitivity analyses removing studies with low-to-moderate risk of bias, removing data imputed from continuous measures, and removing studies with individuals with diagnoses other than schizophrenia, provided similar results, with only the latter showing a reduction of heterogeneity (I^2 from 59% to 5%). We were able to perform meta-regression analyses for relatively few variables, as reporting was generally poor. We did not find a moderating effect of mean age, mean illness duration, and country income (see eAppendix, Supplement 6). However, we observed a trend towards a stronger association between ACE exposure and suicide behavior in studies with a higher proportion of female participants, although statistical significance was not reached (p = 0.070) (Fig. 3).

Secondary outcomes are summarized in Table 2 and extensively reported in the eAppendix (Supplement 7). We pooled the most adjusted ORs describing the association between CTQ-SF scores and the probability of suicide behavior, finding a positive association (OR 1.04; 95% CI 1.02 to 1.07). Similarly, a positive association was found between exposure to ACEs and suicidal ideation (OR 2.47; 95% CI 1.94 to 3.14), suicide attempt (OR 1.83; 95% CI 1.40 to 2.40), while only one study reported data on suicide death (OR 4.24; 95% CI 1.15 to 15.59), and only two studies on non-suicidal self-injury (OR 1.77; 95% CI 1.10 to 2.85). The association with any suicide behavior persisted for any subtype of ACEs, namely physical abuse (OR 1.51; 95% CI 1.19 to 1.93), physical neglect (OR 1.83; 95% CI 1.23 to 2.73), emotional abuse (OR 1.97; 95% CI 1.37 to 2.83), emotional neglect (OR 1.82; 95% CI 1.03 to 3.21), and sexual abuse (OR 1.66; 95% CI 1.15 to 2.39).

4. Discussion

The present meta-analysis of observational studies explored the association between ACEs and suicide behaviors and non-suicidal self-injury in individuals with SSD and demonstrated a relevant association for any suicide behavior in people with SSD, with a probability almost doubled (about 92% higher) in individuals exposed compared to those

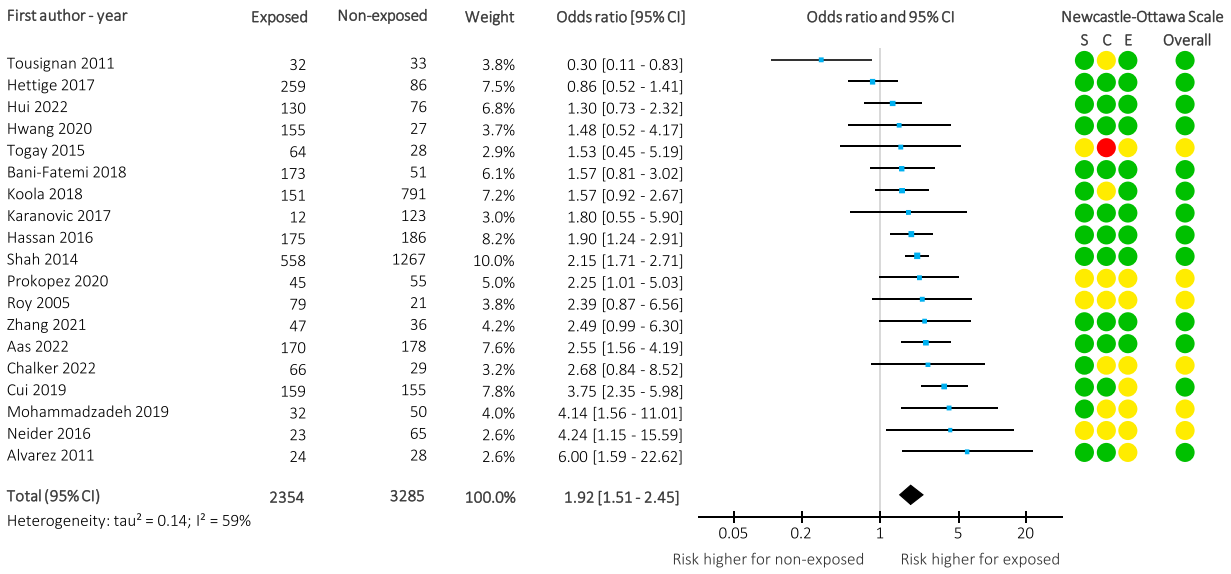

Fig. 2. Forest plot for the probability of suicide behavior in individuals with schizophrenia spectrum disorders exposed or non-exposed to adverse childhood events. *S*=Selection; C=Comparability; *E*=Exposure/outcome; CI=Confidence Interval.

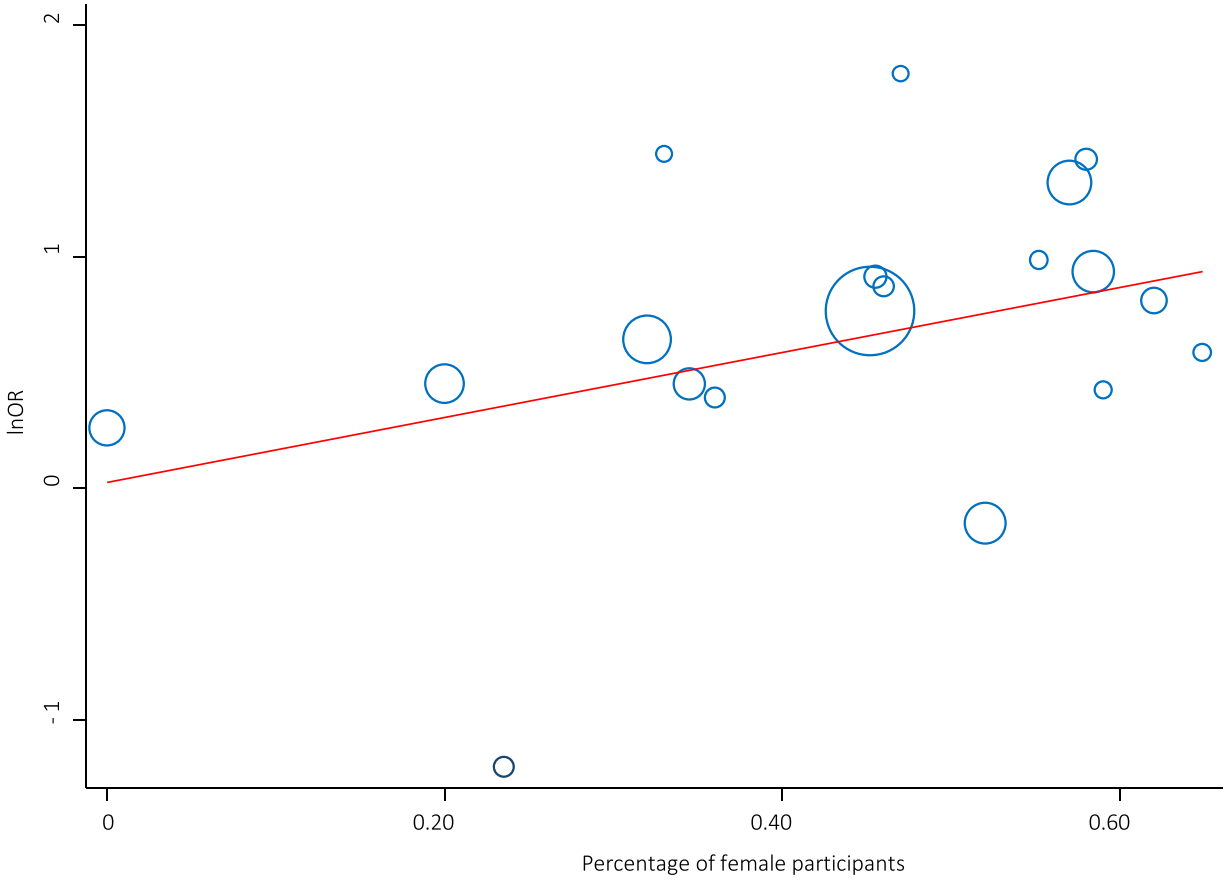

Fig. 3. Association between the probability of suicide in individuals with SSD exposed to ACEs and the proportion of female participants. Each circle represents a study and its radius is proportional to the sample size. The red line represents the regression. lnOR=natural logarithm of the odds ratio.

unexposed. Statistically, this association is strong, and falls into the "Highly Suggestive" (Class II) category according to umbrella review criteria, further enhancing results reliability. The finding that ACE severity was positively associated with the probability of suicide behavior adds plausibility and further corroborates the main study result.

When considering different types of suicide behavior separately, the probability appeared to be higher for suicide ideation (increased by 147% in those exposed) than for suicide attempt (increased by 83%), while data on non-suicidal self-injury and death by suicide were reported by only two and one studies, respectively, and their interpretation is therefore imprecise. These figures expand findings from the

Table 2
Results of secondary analyses.

Analysis	N. studies	N. participants	Exposed to ACEs	Non-exposed to ACEs	OR (95% CI)	I^2
Probability of suicide behavior as a function of the CTQ-SF score	6	1334	820	514	1.04 (1.02 to 1.07)	69%
Suicidal ideation in individuals exposed to any ACEs	7	2681	1062	1619	2.47 (1.94 to 3.14)	14%
Suicide attempt in individuals exposed to any ACEs	15	4345	1987	2358	1.83 (1.40 to 2.40)	61%
Suicide death in individuals exposed to any ACEs	1	88	23	65	4.24 (1.15 to 15.59)	NA
Non-suicidal self-injury in individuals exposed to any ACEs	2	1149	329	820	1.77 (1.10 to 2.85)	0%
Any suicide behavior in individuals exposed to physical abuse	12	2690	856	1834	1.55 (1.21 to 1.99)	22%
Any suicide behavior in individuals exposed to physical neglect	8	1492	730	762	1.83 (1.23 to 2.73)	52%
Any suicide behavior in individuals exposed to emotional abuse	13	1931	850	1081	1.97 (1.37 to 2.83)	52%
Any suicide behavior in individuals exposed to emotional neglect	10	1656	554	1102	2.82 (1.03 to 3.21)	78%
Any suicide behavior in individuals exposed to sexual abuse	12	2650	793	1857	1.66 (1.15 to 2.39)	57%

ACE=Adverse Childhood Event; CI=Confidence Interval; CTQ-SF=Childhood Trauma Questionnaire Short Form; OR=Odds Ratio; NA=Not Available.

general population (Grummitt et al., 2021) and other populations with mental illness, such as severe affective disorders (Park et al., 2020). Interestingly, meta-regression analyses showed a trend toward higher probability in females, which is in line with existing literature (Comacchio et al., 2019).

Secondary analyses showed that all ACEs subtypes were associated with an increased probability of suicide behaviors, nearly doubled for those exposed to most ACEs, except for physical and sexual abuse, for which the risk increased to a lesser extent (by 51% and 66%, respectively). Meta-analytical evidence in the population of prisoners showed a similar magnitude of association, with no relevant differences between ACEs subtypes (Angelakis et al., 2020). However, most of the existing literature focuses on trauma in general, including heterogeneous subtypes of ACEs, which might affect psychopathology and disease trajectories differently. For instance, some studies found that emotional abuse, which includes belittling, blaming, and frightening patterns, is associated with greater post-traumatic stress disorder (PTSD) and depressive symptom severity compared to other types of childhood trauma (Gama et al., 2021; Li et al., 2022).

Furthermore, ACEs might increase the risk of suicidal behavior also indirectly, as the available evidence suggests that exposure to multiple ACEs linearly increases the risk and severity of positive psychotic symptoms (Croft et al., 2019), which are in turn associated with increased suicidality (DeVylder et al., 2015; Nishida et al., 2014).

The mechanism that underlies the association between ACEs and suicidal behaviors is complex and multifactorial. Parents and caregivers play a critical role in structuring, elaborating, and regulating a child's emotions (Alink et al., 2012). In turn, children exposed to trauma may perceive the world as unpredictable and are not emotionally available to provide the required structure and regulation of emotions (Kim and Cicchetti, 2006). This might increase the risk of more severe psychopathology, peer rejection, interpersonal difficulties, and ultimately suicidal thoughts and behaviors (Shipman et al., 2005).

Moreover, PTSD has been clearly associated with both childhood trauma (Crede et al., 2023) and suicidal behaviors (Akbar et al., 2023), and might therefore moderate the effect of ACEs on suicide, although this remains speculative, given the lack of assessment and reporting of PTSD in studies included in this review.

There is agreement that ACEs exposure can sensibly increase the risk of suicide. However, comparing the magnitude of such an effect between people with SSD and other mental health conditions is problematic. Some of the largest studies on depressed and bipolar individuals showed a risk increase around 45% in those exposed to ACEs (Farias et al., 2019; Gloger et al., 2021). This might suggest that individuals with SSD are particularly vulnerable to ACEs exposure compared to populations with affective disorders, although this interpretation remains speculative.

Several limitations should be highlighted. First, most of the included studies employed a retrospective study design. We acknowledge that this design may expose a risk of recall bias for both exposures to traumatic events and suicide behavior. Further, data of interest were often incompletely reported. Although we were able to retrieve and impute several missing data, these were not adjusted for potential socio-demographic and clinical confounders, limiting the confidence in the estimates. We attempted to manage this limitation by performing several meta-regression analyses to explore possible effect mediators, however, data from original studies were often lacking. Second, the included primary studies recruited relatively heterogeneous populations in terms of baseline diagnoses. Indeed, the moderate heterogeneity found in the primary analysis (I^2=61%) dropped in the sensitivity analysis including only people affected by schizophrenia (I^2=5%). For this population the risk of any suicide behavior was increased by 150% in exposed individuals, possibly suggesting a higher risk for those with schizophrenia compared with other diagnoses within the SSD. Third, several studies did not provide data suitable for meta-analyses. We were able to impute data according to a validated methodology for most of them. Although imputation methodologies are based on assumptions (e.g., the clinical relevance of certain rating scale cut-offs), a sensitivity analysis removing imputed data was consistent with the primary analysis. Still, the relevant amount of missing data limited the interpretation of important sensitivity analyses, such as for the outcomes of suicides death and non-suicidal self-injury. Fourth, although we analyzed different ACE subtypes separately, we are aware that most individuals were probably exposed to multiple co-occurring traumatic experiences, which we were not able to disentangle to be considered separately. Fifth, non-suicidal self-injury might be a relevant and often underestimated issue in people with schizophrenia-spectrum disorders (Lorentzen et al., 2022), however, whether and how this occurrence is associated with ACEs can be hardly derived by the evidence included in this review, possibly due to the lack of assessment and reporting.

Despite the limitations highlighted, these results have relevant implications for clinical practice and policy. Screening for ACEs in individuals with SSD should be added to the list of information routinely collected about the person's medical history and past home and social situation. We suggest that the screening process might be complemented using simple validated questionnaires, such as the CTQ-SF, which may better characterize the types and severity of ACEs suffered. In case ACEs are identified, mental health professionals should regularly monitor the patient for the onset or aggravation of current risk factors for suicide behaviors and activate psychosocial support interventions targeting the psychological consequences of ACE exposure whenever possible. In terms of policy implications, universal, selected, and indicated prevention programs targeting vulnerable populations should be implemented to minimize exposure to ACEs and associated risks on several mental health outcomes, including suicide.

To further improve the quality of evidence, and its applicability to clinical practice, large database analyses prospectively comparing individuals exposed and unexposed to ACEs would be of epidemiological relevance, as they would allow overcoming the issue of recall bias. Moreover, future studies should take into due account the effect of different types of ACEs, and how they co-occur and interplay in determining suicide behaviors and non-suicidal self-injury.

In this meta-analysis of observational studies, we have found

compelling evidence suggesting that ACE exposure increases the risk of suicide behaviors in patients with SSD, with a risk almost doubled for individuals exposed as compared with those unexposed. This association was confirmed for suicidal ideation, suicide attempts, and for different types of ACEs. These findings suggest that actively investigating and characterizing ACEs in individuals with SSD is a key step to improving and tailoring suicide risk assessment and management in individuals with SSD. Evidence-based clinical guidelines should be updated accordingly.

Declaration of Competing Interest

M. Solmi received honoraria/has been a consultant for Angelini, Lundbeck, Otsuka. The other authors have no conflicts of interest to declare.

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Supplementary materials

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