Dear Author

Please use this PDF proof to check the layout of your article. If you would like any changes to be made to the layout, you can leave instructions in the online proofing interface. First, return to the online proofing interface by clicking "Edit" at the top page, then insert a Comment in the relevant location. Making your changes directly in the online proofing interface is the quickest, easiest way to correct and submit your proof.

Please note that changes made to the article in the online proofing interface will be added to the article before publication, but are not reflected in this PDF proof.

Neuropsychobiology

Systematic Review

Neuropsychobiology
DOI: 10.1159/000542392

Received: May 20, 2024
Accepted: September 20, 2024
Published online: November ▪▪▪, 2024

Adverse Childhood Experiences Are Associated with Mental Health Problems Later in Life: An Umbrella Review of Systematic Review and Meta-Analysis

Biruk Beletew Abate[a, b] Ashenafi Kibret Sendekie[c, d] Abebe Merchaw[e]
Gebremeskel Kibret Abebe[e] Molla Azmeraw[e]
Addis Wondmagegn Alamaw[e] Alemu Birara Zemariam[e]
Tegene Atamenta Kitaw[e] Amare Kassaw[f] Tilahun Wodaynew[e]
Ayelign Mengesha Kassie[b] Gizachew Yilak[e] Mulat Awoke Kassa[a, g]

[a]School of Population Health, Curtin University, Bentley, WA, Australia; [b]College of Medicine and Health Sciences, Woldia University, Woldia, Ethiopia; [c]Department of Clinical Pharmacy, School of Pharmacy, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia; [d]School of Pharmacy, Curtin Medical School, Faculty of Health Sciences, Curtin University, Bentley, WA, Australia; [e]Department of Nursing, College of Health Science, Woldia University, Woldia, Ethiopia; [f]College of Health Science, Debre Tabor University, Debre Tabor, Ethiopia; [g]College of Health Sciences, Woldia University, Woldia, Ethiopia

Keywords
Adverse childhood experience · Adversity · Mental Health Problems · Umbrella review

Abstract

Introduction: Evidence suggested a link between early adversity and mental health problems. However, it is unclear how much adverse childhood experiences (ACEs) contribute to mental health problems because researchers have produced inconsistent findings. Therefore, the objective of this umbrella review was to combine the contradictory data regarding the effect of ACEs on the development of mental health problems later in life in the global context. ***Methods:*** PubMed, Embase, Scopus, Web of Sciences, Cochrane Database of Systematic Reviews, Scopus, and Google Scholar which reported the effect of ACEs on the development of mental health problems was searched. The quality of the included studies was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR). A weighted inverse variance random-effects model was applied to find the pooled estimates. The subgroup analysis, heterogeneity, publication bias, and sensitivity analysis were also assessed. ***Results:*** Forty-three SRM with 14,707,614 study participants were included. The pooled effect of ACEs on the development of mental health problems later in life in the global context is found to be (AOR = 1.66 [1.46, 1.87]). Subgroup analysis based on country revealed (AOR = 1.67 [1.23, 2.11]) in UK, (AOR = 0.61 [0.41, 0.81]) in Canada, (AOR = 1.55 [1.40, 1.69]) in Brazil, (AOR = 5.65 [4.12, 7.18]) in Ethiopia, (AOR = 1.92 [1.45, 2.38]) in USA, (AOR = 2.30 [1.89, 2.72]) in Australia, and (AOR = 1.66 [1.46, 1.87]) in Ireland. While subgroup analysis based on types of adverse childhood adverse experience: domestic violence ([AOR = 4.13 [1.96, 6.30]),

karger@karger.com
www.karger.com/nps

Correspondence to:
Biruk Beletew Abate, birukkelemb@gmail.com

Karger

maltreatment (AOR = 1.5 [0.79, 2.21]), physical abuse(AOR = 1.56 [1.43, 1.63]), sexual abuse (AOR = 2.07 [1.63, 2.51]), child abuse (AOR = 5.66 [4.12, 7.18]), parental mental health problem (AOR = 1.73 [1.39, 2.08]), bullying (AOR = 1.99 [1.69, 2.29], neglect (AOR = 2.11 [1.53, 2.69]), and parental divorce (AOR = 1.66 [1.46, 1.87]). Based on the type of mental health problem, the pooled effect size is 1.87 (1.45, 2.30) for depression and 1.67 (1.22, 2.13) for anxiety. ***Conclusion:*** This umbrella review revealed that ACE is significantly associated (with 66% increased risk) with anxiety and depression later in life in a global context. This association is most noticeable when one is subjected to domestic violence, maltreatment, physical abuse, sexual abuse, child abuse, parental mental health problems, bullying, neglect, and parental divorce. Childhood periods are a critical window of opportunity for reducing the risk of developing mental illness in the future and for implementing intervention measures. Preventing childhood maltreatment and addressing psychiatric risk factors can prevent psychopathology. Longitudinal studies are needed to optimize healthcare responses to ACEs. Increased awareness and public health interventions are needed to prevent childhood adversity and prevent mental problems among these victims. To optimize healthcare responses to unfavorable outcomes of childhood adversities, longitudinal and intervention research findings, more public health initiatives, and awareness are required.

Introduction

Adverse childhood experiences (ACEs) are stressful and perhaps traumatic events that occur during infancy or adolescence (0–18 years old), and they can negatively impact a person's health and well-being [1, 2]. Adversity in the form of childhood abuse, parental mental illness, dysfunctional families, violence, and socioeconomic hardship are all considered ACEs. ACEs are common across low-, middle- and high-income countries, with two in every five adults having at least one ACE [1, 2]. Adverse childhood experiences, such as abuse, neglect, and dysfunctional households before the age of eighteen, are linked to poor mental and physical health throughout life, as well as substantial societal financial consequences [3, 4].

Individual studies have demonstrated that parent ACEs are associated with a range of outcomes in their offspring, such as a higher risk of developmental delay, a difficult temperament, and emotional and behavioral challenges, through a variety of direct and indirect biological, psychological, biophysical, and behavioral pathways [4]. Childhood maltreatment significantly contributes to depression and anxiety disorders in children and adults through various neurobiological mechanisms, structural brain differences, functional brain differences, and genetics and epigenetics of resilience and vulnerability [5, 6]. Childhood maltreatment poses a threat to the optimal development of affective processing skills, attachment bonds, self-system functions, peer interactions, and school adaptability [7, 8]. Depression and anxiety disorders are the major causes of psychiatric morbidity worldwide [9]. Depressive disorders, accounting for 42.5% of mental illness and substance use disorders, and 15.3% of anxiety disorders, accounted for 40.5% of disability-adjusted life years in 2010 [10, 11]. Childhood maltreatment is linked to various psychiatric disorders like depression, anxiety, psychosis, suicidality, ADHD, conduct disorder, and substance abuse, as consistently shown in previous reviews and meta-analyses [12, 13].

Because of their upbringing, children who are subjected to abuse and neglect may be more vulnerable to mental health problems. However, additional genetic and environmental risk factors for mental health conditions may enhance their risk and mask previously found associations. For example, studies show that children who have been abused are more likely to have family histories of mental illness and higher polygenic scores for psychiatric disorders (such as depression and schizophrenia) [14, 15]. Maltreated children are also prone to face additional environmental hazards for mental health issues, such as socioeconomic difficulties and bullying victimization. Unfortunately, these co-occurring risk variables have not been properly considered in most previous studies on maltreatment and mental health. The standard epidemiological techniques used in these investigations, such as multiple regression, have limited ability to account for genetic impacts or other unmeasured confounders [16, 17]. Finally, researchers have found that people who reported more ACEs were more likely to report poor or fair health [18, 19] or a lower sense of well-being [20], have poorer access to medical/mental health services [19, 21], be less satisfied with their lives [22], and die prematurely by as much as 20 years earlier [20, 23], than people who reported fewer ACEs. Researchers have found a relationship between the number of ACEs and learning and behavioral problems among children and adolescents [24, 25], and somatic disorders, hallucinations, anxiety and obsessive-compulsive disorders, depression, and suicide attempts among adults [18, 19, 26]. People with repeated traumas and the ensuing emotional dysregulation may exhibit symptoms of dissociation and

heightened automatic response in post-traumatic stress disorder [27, 28].

Evidence suggested a link between early adversity and mental health problems. However, it is unclear how much ACEs contribute to mental health problems because research has produced inconsistent findings. Therefore, the objective of this umbrella review was to combine the contradictory evidence regarding the effect of ACEs on the development of mental health problems later in life in a global context.

Methods

This umbrella review was done following the methodology of umbrella review of existing SRM studies [29]. From checking PROSPERO, this umbrella review wasn't registered. It was undertaken through a systematic synthesis of the eligible SRM reports on the effect of ACEs the development of mental illnesses later in life in a global context.

Searching Strategy and Information Sources

We used PICO frameworks to search PubMed, Embase, Scopus, Web of Sciences, Cochrane Database of Systematic Reviews, and Google Scholar for studies that provided information on the estimate of the effect of ACEs on the development of mental illnesses later in life. To get more papers, the search was conducted using MeSH terms and keywords, combinations, and snowball searching in the references list of articles that were found using the database search. For each condition, three concepts and key search terms were identified and used to develop search strategies. Concept 1: "Adverse childhood experience," "childhood adversity," "domestic violence," "mmaltreatment," "physical abuse," "sexual abuse," "child abuse," "parental mental ilness," "bullying," "neglect," and "parental divorce." Concept 2: "mental health problems," "anxiety," "depression." Concept 3: meta-analysis', "systematic review," and "review." The literature search was done by two reviewers independently, with discrepancies resolved by consensus. Articles with incomplete reported data were handled by contacting corresponding authors. We used the search terms independently and/or in combination using "OR" or "AND" (["adverse childhood experience" OR "childhood adversity" OR "domestic violence" OR "maltreatment" OR "physical abuse," "sexual abuse" OR "child abuse" OR "parental mental ilness" OR "bullying" OR "neglect" OR "parental divorce"]) AND ("mental health problems" OR "anxiety" OR "depression") AND ("risk factor" OR "predictor" OR cause' OR determinant') AND (meta-analysis' OR "systematic review" OR "review").

A sample of the literature search strategy, PubMed search strategy, developed using a combination of MeSH terms and free texts is presented as a supplementary file (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000542392). In addition to the systematic database searching, article searching was done using the reference list of the included studies and the "cited by" and "related articles" functions of PubMed.

Study Selection/Eligibility Criteria

Retrieved SRM were exported to reference manager software, Endnote version 8 to remove duplicate studies. Two investigators (B.B.A. and M.A.) independently screened the selected studies using their titles and abstracts before retrieval of full-text papers. We used prespecified inclusion criteria to further screen the full-text articles. Those SRM had reported the effect of childhood adversity as a risk factor for mental health problems in the English language in a global context. For a study to be considered a systematic review or meta-analysis, it should have to meet the following predefined criteria: (a) present a defined literature search strategy, (b) appraise included studies using a relevant tool, and (c) follow a standard approach in pooling studies and providing summary estimates. Studies were excluded due to any of the following reasons: (a) no report on the measures of interest for this study, (b) language other than English, and (c) narrative reviews, editorials, correspondence, abstracts, and methodological studies. The screening and selection of studies were conducted in two stages. First, title and abstract screening was done and then, full-text reviewing was done. Disagreements were discussed during a consensus meeting with other reviewers for the final selection of studies to be included in the umbrella review [30].

Quality Assessment

The methodological quality of all included reviews was assessed by two independent reviewers using the Assessment of Multiple Systematic Reviews (AMSTAR) tool [31, 32]. It consists of 11 questions that measure the quality of the approaches used for pooling the empirical studies included in the review and summarizing their estimates. The tool has been validated and frequently used for appraisal of the quality of SRM works. The quality scoring was done out of 11, with scores 8–11, 4–7, and < 3 indicating high, medium, and low qualities, respectively. The decision as to whether to include a review can be made based on meeting a pre-determined

Table 1. Distribution of included reviews on the effect of ACEs on mental health problems later in life in a global context

Ser No	Author	Year	Country	No of included studies	Sample size	Effect size	SE	Types of ACE	Types of MHP
1	Trevillion et al. [2]	2012	UK	13	21,355	2.77 (1.96, 3.92)	0.5	Domestic violence	Depression
2	Trevillion et al. [2]	2012	UK	7	21,355	4.08 (2.39, 6.97)	1.17	Domestic violence	Anxiety
3	Trevillion et al. [2]	2012	UK	4	21,355	7.34 (4.5, 11.98)	1.91	Domestic violence	Mental health problems (unspecified)
4	Baldwin et al. [34]	2023	UK	34	54,646	0.31 (0.24, 0.37)	0.03	Maltreatment	Mental health problems (unspecified)
5	Racine et al. [35]	2023	Canada	52	14,570	0.17 (0.12, 0.21)	0.02	Multiple ACE	Mental health problems (unspecified)
6	Gallo et al. [36]	2018	Brazil	3	20,021	2.53 (1.26, 5.09)	0.98	Physical Abuse	Depression
7	Gallo et al. [36]	2018	Brazil	3	20,021	1.55 (1.33, 1.81)	0.12	Physical abuse	Depression
8	Gallo et al. [36]	2018	Brazil	3	20,021	2.14 (1.11, 4.15)	0.78	Sexual abuse	Depression
9	Gallo et al. [36]	2018	Brazil	3	20,021	1.5 (1.25, 1.8)	0.14	Sexual abuse	Depression
10	Gallo et al. [36]	2018	Brazil	3	20,021	1.75 (1.36, 2.25)	0.23	Physical abuse	Anxiety
11	Gallo et al. [36]	2018	Brazil	3	20,021	1.51 (1.14, 1.98)	0.21	Physical abuse	Anxiety
12	Gallo et al. [36]	2018	Brazil	3	20,021	1.7 (1.23, 2.37)	0.29	Sexual abuse	Anxiety
13	Gallo et al. [36]	2018	Brazil	3	20,021	1.18 (0.74, 1.87)	0.29	Sexual abuse	Anxiety
14	Jonas et al. [37]	2022	UK	27	199,285	0.55 (0.38, 0.71)	0.08	Multiple ACE	Mental health problems (unspecified)
15	Mitiku et al. [38]	2023	Ethiopia	14	3,254	5.65 (4.32, 7.39)	0.78	Child abuse	Mental health problems (unspecified)
16	Hughes et al. [39]	2017	UK	13	2,998	4.4 (3.54, 5.46)	0.49	Multiple ACE	Depression
17	Lindert et al. [40]	2014	USA	19	115,579	2.04 (1.65, 2.53)	0.22	Sexual abuse	Depression
18	Lindert et al. [40]	2014	USA	19	115,579	1.49 (1.29, 1.72)	0.11	Physical abuse	Depression
19	Lindert et al. [40]	2014	USA	19	115,579	2.52 (2.12, 2.98)	0.22	Sexual abuse	Anxiety
20	Lindert et al. [40]	2014	USA	19	115,579	1.7 (1.33, 2.18)	0.22	Physical abuse	Anxiety

Table 1 (continued)

Ser No	Author	Year	Country	No of included studies	Sample size	Effect size	SE	Types of ACE	Types of MHP
21	Xiao et al. [41]	2022	UK	90	29,140	0.36 (0.04, 0.69)	0.17	Maltreatment	Mental health problems (unspecified)
22	Ayano et al. [42]	2022	Australia	5	2,878	2.1 (1.656, 2.66)	0.26	Parental mental problem	Anxiety
23	Ayano et al. [42]	2023	Australia	12	2,878	1.95 (1.55, 2.46)	0.23	Parental mental problem	Depression
24	Li et al. [5]	2016	Canada	7	3,151,460	2.03 (1.37, 3.01)	0.42	Maltreatment	Depression
25	Li et al. [5]	2016	Canada	7	3,151,460	2.7 (2.1, 3.47)	0.35	Maltreatment	Anxiety
26	McKay et al. [43]	2020	Ireland	23	5,190	3.11 (1.36, 7.14)	1.47	Maltreatment	Mental health problems (unspecified)
27	Racine et al. [44]	2012	Canada	15	7,914	0.19 (0.13, 0.24)	0.03	Multiple ACE	Depression
28	Varese et al. [45]	2012	Canada	15	7,914	0.23 (0.06, 0.39)	0.08	Multiple ACE	Depression
29	Varese et al. [45]	2012	Canada	15	7,914	0.16 (0.08, 0.23)	0.04	Multiple ACE	Anxiety
30	Varese et al. [45]	2012	Canada	15	7,914	0.11 (0, 0.22)	0.06	Multiple ACE	Anxiety
31	Varese et al. [45]	2012	Canada	28	81,253	2.78 (2.34, 3.31)	0.25	Multiple ACE	Mental health problems (unspecified)
32	Ttofi et al. [46]	2011	UK	28	81,253	1.99 (1.71, 2.32)	0.16	Bullying	Depression
33	Lawrence et al. [47]	2019	UK	25	7,285	1.76 (1.58, 1.96)	0.10	Parental mental problem	Anxiety
34	Lawrence et al. [47]	2020	UK	25	7,285	1.31 (1.13, 1.52)	0.10	Parental mental problem	Depression
35	Agnew-Blais, Danese [48]	2016	UK	30	21,373	1.57 (1.25, 1.99)	0.19	Maltreatment	Anxiety
36	Agnew-Blais, Danese [48]	2016	UK	30	21,373	1.9 (1.39, 2.61)	0.31	Maltreatment	Depression
37	Norman et al. [49]	2012	Australia	124	267,713	1.54 (1.16, 2.04)	0.22	Physical abuse	Depression
38	Norman et al. [49]	2012	Australia	124	267,713	3.06 (2.43, 3.85)	0.36	Emotional abuse	Depression
39	Norman et al. [49]	2012	Australia	124	267,713	2.11 (1.61, 2.77)	0.30	Neglect	Depression
40	Chen et al. [50]	2010	Australia	37	3,162,318	3.09 (2.43, 3.94)	0.39	Sexual abuse	Anxiety

Table 1 (continued)

Ser No	Author	Year	Country	No of included studies	Sample size	Effect size	SE	Types of ACE	Types of MHP
41	Chen et al. [50]	2010	Australia	37	3,162,318	2.66 (2.14, 3.3)	0.30	Sexual abuse	Depression
42	Sands et al. [51]	2016	UK	18	21,581	1.56 (1.31, 1.86)	0.14	Parental divorce	Depression
43	Sands et al. [51]	2016	UK	18	2,472	1.16 (0.98, 1.38)	0.10	Parental divorce	Anxiety

proportion of all criteria, or on certain criteria being met. Decisions about a scoring system or any cut-off for exclusion were made in advance and agreed upon by all reviewers before critical appraisal commences. We have checked the quality of the included primary/original research studies in each of the research syntheses that have been included in the umbrella review [30, 33].

Data Extraction

Data were extracted using a standardized extraction form in Excel sheet created a priori independently to capture and collect relevant information from each included study. The data extraction sheet was piloted using 5 papers randomly, and it was adjusted as needed. One author (B.B.A.) extracted data which were checked by a second author (M.A.). Any disagreements were resolved through discussions, with a third author involved as required (M.A.K.). Data abstraction form, developed in an Excel spreadsheet. For each SRM study, the following data were extracted: (a) identification data (first author's last name and publication year), (b) review aim and type, (c) odds ratio or relative risk with 95% confidence intervals for mental health problem, (d) number of primary studies included within each SRM study and their respective design type, (e) total number of sample size included, (f) publication bias assessment methods and scores, (j) quality assessment methods and scores, (h) data synthesis methods (random or fixed-effects model), and (i) the authors' main conclusion of the SRM study (Table 1).

Statistical Analysis

After the data were extracted using Microsoft Excel format, we imported the data to STATA version 14.0 statistical software for further analysis. Both narrative and qualitative approaches were used to summarize the estimates of the included reviews. When two or more estimates were provided on the same topic, we presented the range of the estimates and calculated a summary (pooled) estimate. Using the binomial distribution formula, standard error was calculated for each study. We pooled the overall estimate estimates of the effect of childhood adversity as a risk factor for mental illness by a random effect meta-analysis [52]. The pooled effect of childhood adversity with 95% CI was presented using forest plots. We examined the heterogeneity between the studies using Cochrane's Q statistics (Chi-square), inverse variance (I^2), and p values [53]. In this study, the I^2 statistic value of zero indicates true homogeneity, whereas the values 25, 50, and 75% represented low, moderate, and high heterogeneity, respectively [32, 54]. For the data identified as heterogeneous, we conducted our analysis by DerSimonian-Laird random-effects model analysis. The subgroup analysis was conducted by economic classification of global countries. Sensitivity analysis was employed to see the effect of a single study on the overall estimation. Publication bias was checked by funnel plot and more objectively through Egger's regression test [55].

Results

A total of 3,388 reviews were identified: 3,380 from differ databases and 3 from other sources. After duplication was removed, a total of 1,428 articles remained (1960 removed by duplication). Finally, 103 studies were screened for full-text review, and 43 SRM with 14,707,614 study participants were included for the final analysis (Fig. 1).

Characteristics of Included Studies

All included reviews were systematic reviews and meta-analyze (SRM). Almost all studies (21/22) were published after 2022. The SRM included individual

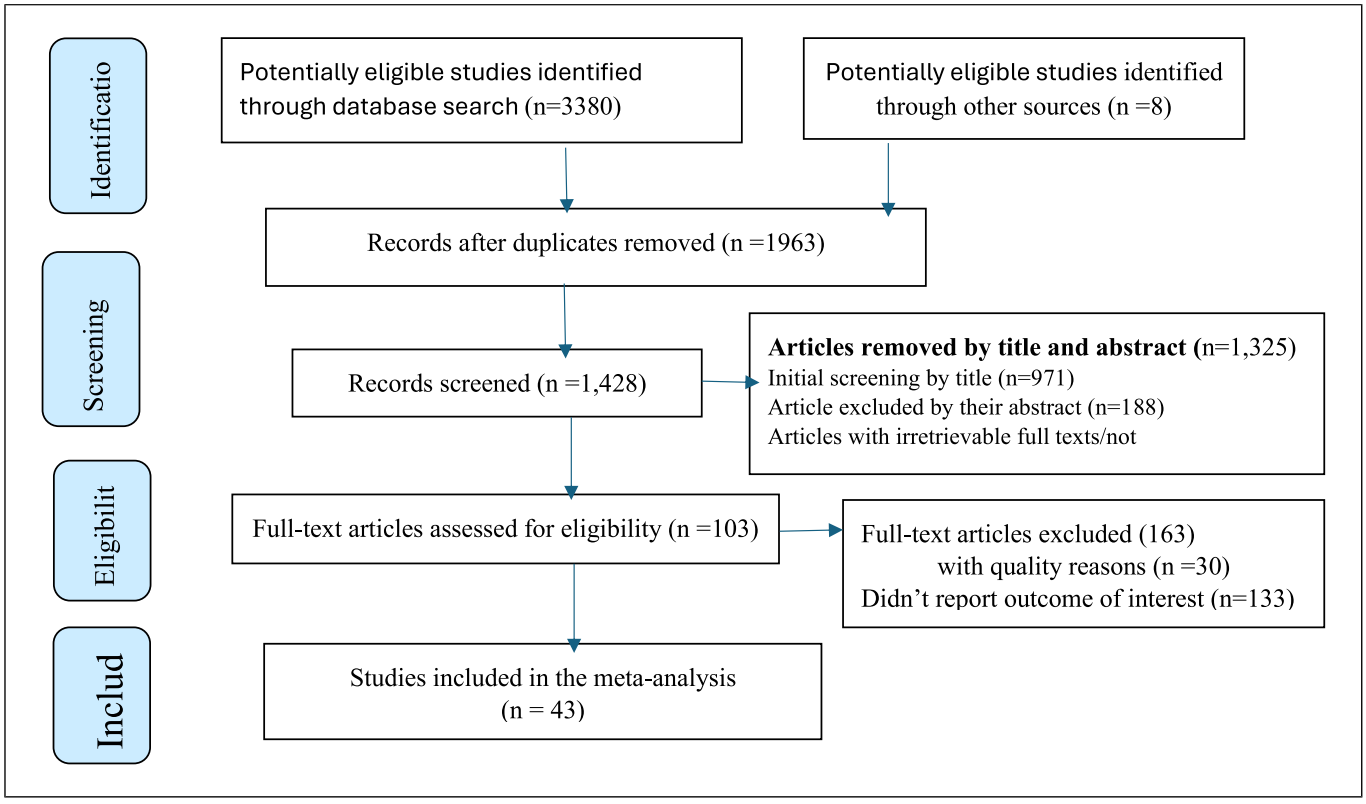


Fig. 1. PRISMA – adapted flow diagram showed the results of the search and reasons for exclusion [56].

studies ranging from 3 to 124. The minimum and maximum sample sizes in these included SRM were 7,914 and 267,713, respectively (Table 1).

Pooled Effect of ACE on the Development of Mental Health Problems

The random-effects model analysis from those studies revealed that the pooled effect of ACE as a risk factor for mental health problems later in life globally is found to be 1.66 (95% CI: 1.46, 1.87) ($I^2 = 97.9\%$; $p < 0.001$). The odds of mental health problems among participants who had a history of ACEs ranged from 0.11 (0, 0.22) in Varese et al. [45] to 7.34 (4.5, 11.98) Trevillion et al. [2] (Fig. 2).

To analyze the pooled effect of ACEs on the development of mental health problems, the included SRM studies adjusted confounding variables including sociodemographic (i.e., child age, parent age, income level, child sex, or racial/ethnic minority status) [35, 36, 38, 42, 46, 47]; child abuse history [38]; physical inactivity, overweight or obesity, diabetes, smoking status, alcohol use, self-rated health, cancer, heart disease, respiratory disease, drug use [39]; comorbid psychiatric disorders, parity, and complications during pregnancy [42, 47].

Subgroup Analysis

Subgroup analysis was done by stratified by country, types of ACEs, and type of mental health problem. Accordingly, the pooled effect of ACE on the development of mental health problems is found to be 1.67 (1.23, 2.11) in the UK, 0.61 (0.41, 0.81) in Canada, 1.55 (1.40, 1.69) in Brazil, 5.65 (4.12, 7.18) in Ethiopia, 1.92 (1.45, 2.38) in USA, 2.30 (1.89, 2.72) in Australia, and 1.66 (1.46, 1.87) in Ireland (Fig. 3).

Based on types of adverse childhood adverse experience: domestic violence (4.13 [1.96, 6.30]), maltreatment (AOR = 1.5 [0.79, 2.21]), physical abuse(AOR = 1.56 ([.43, 1.63]), sexual abuse (AOR = 2.07 [1.63, 2.51]), child abuse (AOR = 5.66 [4.12, 7.18]), parental mental health problem (AOR = 1.73 [1.39, 2.08]), bullying (AOR = 1.99 [1.69, 2.29]), neglect (AOR = 2.11 [1.53, 2.69]), and parental divorce (AOR = 1.66 [1.46, 1.87]) were found to be on the development of mental health problems (Fig. 4). By type of mental health problem: the pooled effect of ACE on the development of depression and anxiety is found to be 1.87 (1.45, 2.30), and 1.67 (1.22, 2.13), respectively (online suppl. Fig. S1).

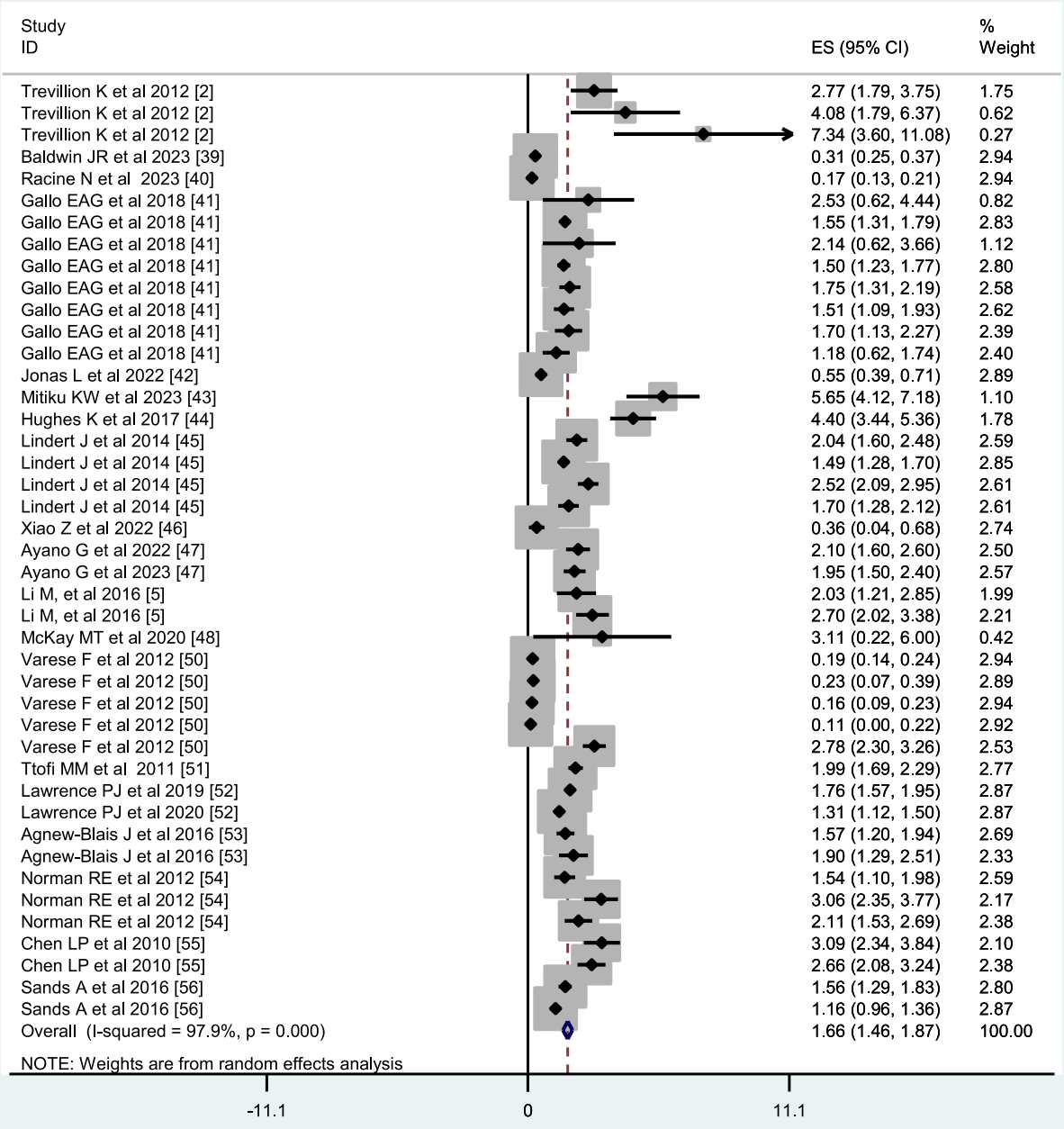
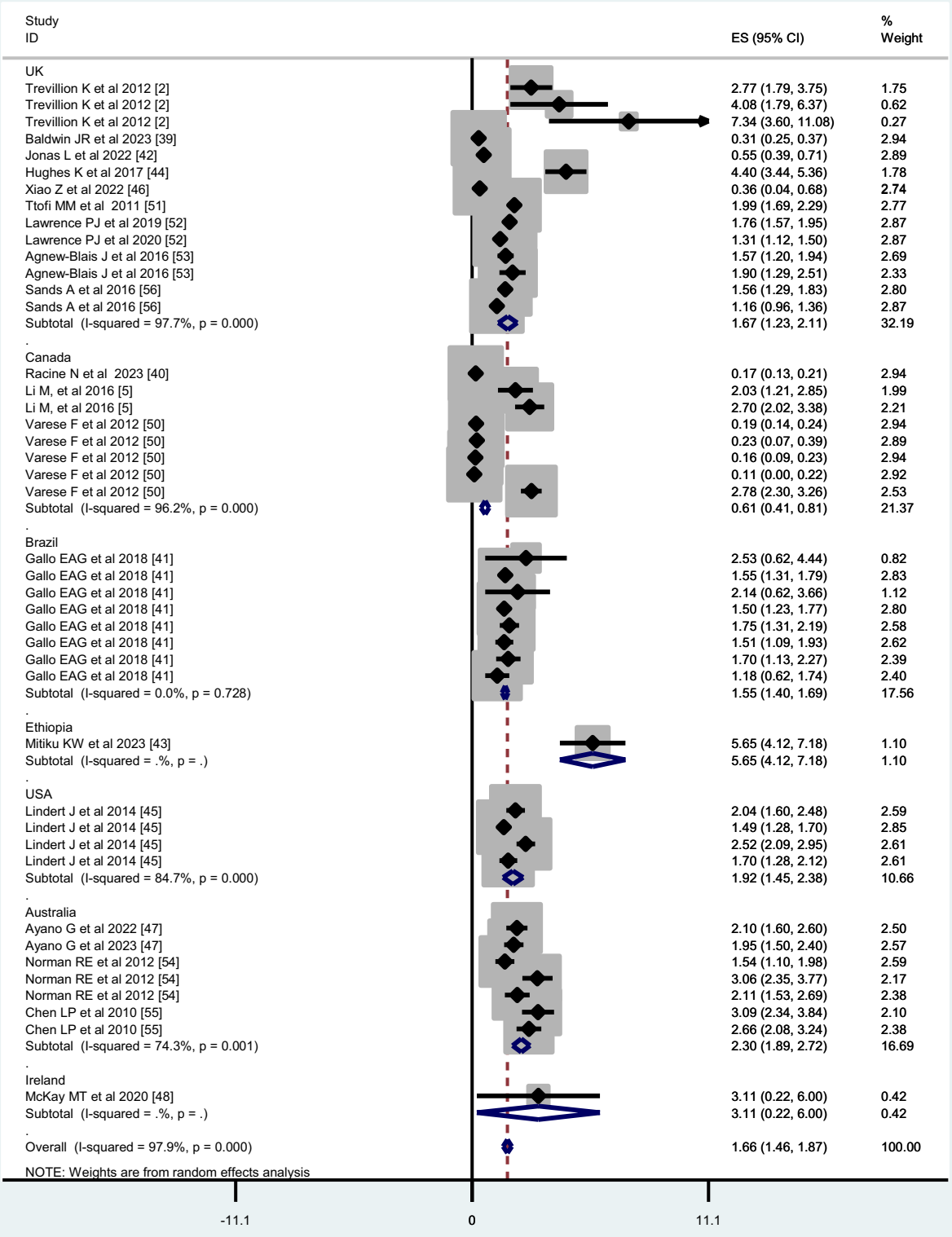


Fig. 2. Forest plot shows the pooled effect of ACE on the development of mental health problems later in life in global context.



3

(For legend see next page.)

Publication Bias and Sensitivity Analysis

Publication Bias

A funnel plot showed asymmetrical distribution (online suppl. Fig. S2). The Egger's regression test value was 0.00, which indicated that, the presence of publication bias (online suppl. Fig. S3). Due to the presence of publication bias, we employed a trim-and-fill analysis. After trim-fill analysis I^2 studies were imputed/filled and the pooled effect became 3.68 (3.05, 4.44) (online suppl. Fig. S4).

Sensitivity Analysis

A leave-one-out sensitivity analysis was employed to identify the impact of the individual study on the pooled acceptance effect size. The results of this sensitivity analysis showed that the pooled finding was not dependent on a single study and there is no influential study (online suppl. Fig. S5).

Discussion

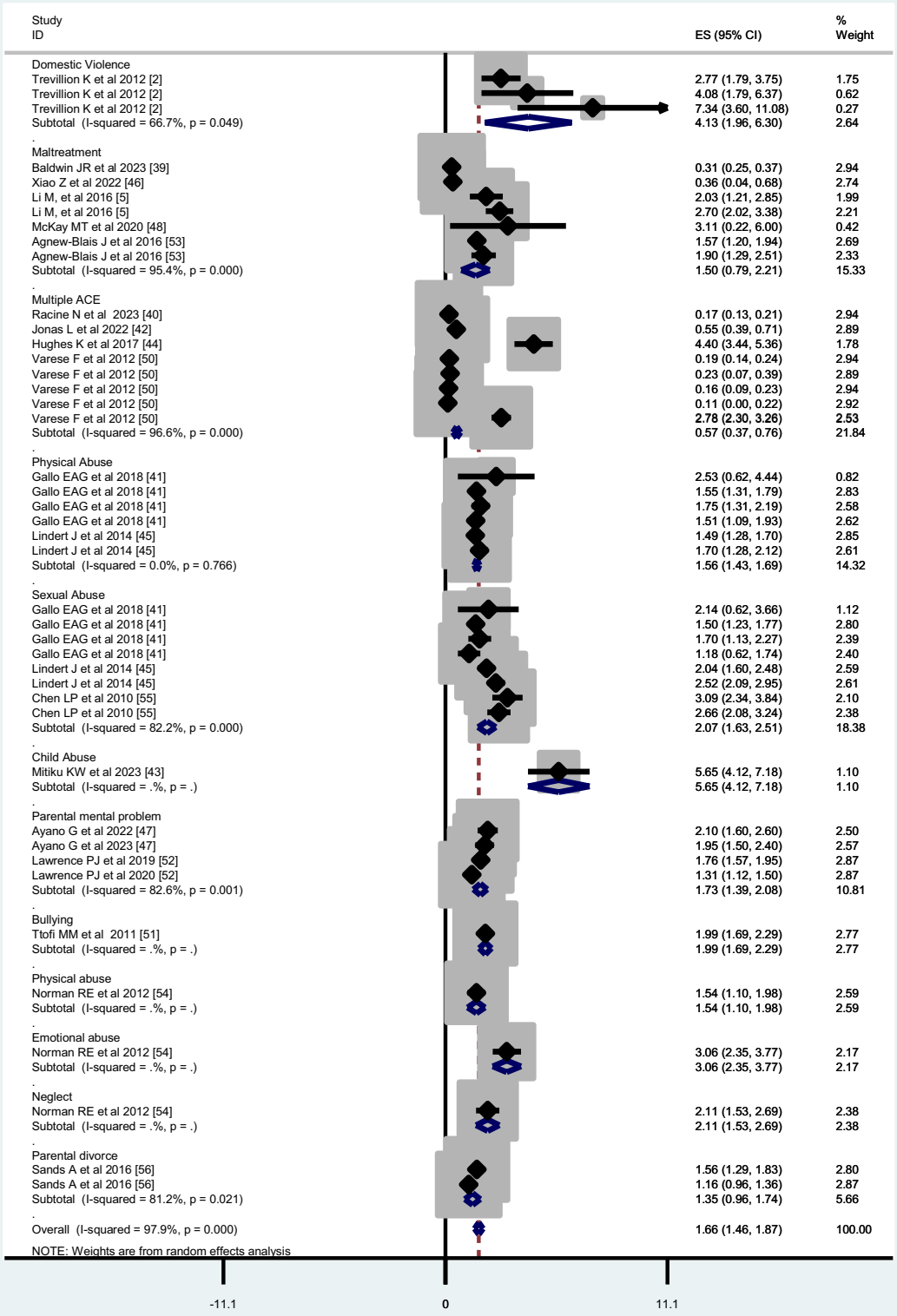
ACEs can result from children experiencing physical, emotional, or sexual abuse, bullying, caregiver neglect, mental illness, drug use in the home, exposure to domestic violence, and parent loss [57–60]. ACEs can cause mental and physical disorders, including post-traumatic stress disorder, depression, and personality disorders, in adult life [58, 59]. Furthermore, survivors of ACEs exhibit reduced resilience in psychiatry later in life and negatively impact resilience in adulthood [57]. According to research, 63% of people who had experienced negative things in the past were less resilient as adults [61].

In the current umbrella review, the random-effects model analysis from those studies revealed that the pooled effect of ACE as a risk factor for mental health problems later in life globally is found to be 1.66 (95% CI: 1.46, 1.87). This finding is in line with previous studies [1, 39, 40, 62, 63]. Those who had four or more ACEs were more likely to be examined later in life for all outcomes (health-harming behaviors and infectious and non-communicable diseases) [39]. ACEs, such as stress or trauma, can alter brain regions responsible for fear, stress reactions, and emotion regulation, potentially increasing the risk of mental health issues later in life [64]. The brain's adaptation to stressful environments may cause abnormalities in mental health, impairing the development of the prefrontal cortex and hippocampus, crucial for memory, and reasoning [65]. Adults who experienced physical or sexual abuse as children have been found to have higher levels of anxiety, despair, and distress as well as a variety of adult psychiatric diagnoses, adverse psychosocial consequences, and poor physical health outcomes [40, 66]. Furthermore, studies have shown that children's growing brains undergo structural and functional changes when they experience severe, frequent, or persistent adversity without the safety net of a caring caregiver. Numerous problems, including an elevated propensity for risky conduct, an excessive stress response, poor executive functioning, and trouble establishing healthy relationships, might result from this [67, 68].

This finding may be explained by the fact that stressful or traumatic experiences can change brain regions that regulate fear, stress reactions, and emotion regulation. These neurological effects can also raise the risk of mental health issues later in life if these ACEs are not recognized and addressed early on [64]. The fact that the individual's brain may have changed to adapt to living in a stressful or fearful environment could also be a contributing factor in this discovery. The prefrontal cortex and hippocampus parts of the brain, which are important in memory and logical cognitive processes, may develop less as a result, which could lead to abnormalities in the person's mental health [65].

Subgroup analysis of the pooled effect size of ACE as a risk factor for mental health problems is almost consistent across different countries. For example, 1.67 (1.23, 2.11) in UK, 1.55 (1.40, 1.69) in Brazil, 1.92 (1.45, 2.38) in USA, 2.30 (1.89, 2.72) in Australia, and 1.66 (1.46, 1.87) in Ireland, However, a study done in Ethiopia revealed that pooled effect of ACE as a risk factor for mental health problem later in life was significantly higher than other countries (5.65 [4.12, 7.18]). Contrary to this result a study done in Canada revealed that the pooled effect of ACE as a risk factor for mental health problems later in life was significantly lower than in other countries 0.61 (0.41, 0.81). This higher pooled effect size in Ethiopia may be explained by the fact that, in contrast to other nations, less intervention had previously been carried out in Ethiopia for children who had a history of traumatic childhood experiences. On the contrary, the government of Canada has implemented crucial interventions for children who have a history of traumatic childhood experiences, which can lessen or mitigate the likelihood of developing mental health issues later in life. This could be the cause of the significantly lower pooled effect size in Canada [69, 70].

Fig. 3. Forest plot shows subgroup analysis of the pooled effect of ACE on the development of mental health problems later in life by country in a global context.



4

(For legend see next page.)

Research shows that adverse childhood events, such as domestic abuse, increase the likelihood of future mental health issues by 4.13 times [2, 71, 72]. Domestic violence increases stress, fear, and isolation in victims, increasing their risk of developing mental health issues, particularly depression. Additionally, victims may internalize the violence, placing responsibility on themselves [73]. Compared to children without a history of maltreatment, individuals with a history of maltreatment had a 1.5-fold higher chance of experiencing mental health issues in the future. Several investigations agree with this finding [34, 74, 75]. A child's history of repeated maltreatment creates a harsh environment, leading to cognitive distortion and an increased risk of mental health problems like depression. Physical abuse increases the likelihood of mental health problems in children, supported by other studies [75, 76]. Physical abuse can lead to reduced risk-taking inhibitions, increasing substance misuse, criminal behavior, and bullying, which are risk factors for mental health issues in later life [77]. Children who have experienced sexual abuse are 2.07 times more likely to experience future mental health issues compared to those without a history of sexual abuse [75, 78]. Childhood sexual abuse can lead to chronic stress, brain damage, and increased mental health issues. It may also be linked to early life challenges like extreme poverty or dysfunctional households [79]. Those who had experienced child maltreatment in the past were 5.55 times more likely to experience mental health issues in the future than those who had not. This conclusion was corroborated by several studies [75, 76, 78]. Early abuse in children may lead to brain development issues such as decreased prefrontal cortex, altered hippocampal formation, and altered corpus callosum, increasing susceptibility to mental health issues [80]. Research indicates that children with a parent's mental illness are 1.73 times more likely to experience mental illness in their lifetime [1, 81]. The reason might be due to genetic predisposition [82]. The second reason could be that parents with mental illnesses may have bad habits or maladaptive behaviors, such as using drugs, alcohol, cigarettes, or marijuana as a form of self-medication. Children raised in such environments may be more likely to adopt these bad habits, which can raise their risk of developing mental health issues in the future [83]. Previous bullying has been linked to a 1.99 times higher likelihood of future mental health issues in children, as supported by multiple investigations [84–86]. Bullying often causes children to experience anger, bitterness, vulnerability, helplessness, frustration, loneliness, and mistrust, leading to aggression and substance abuse as coping mechanisms [87]. Compared to children without a history of neglect, individuals with a history of neglect were 2.11 times more likely to experience mental health issues in the future. Several investigations corroborated this conclusion [49, 62, 74]. The reason could be that neglect throughout childhood disrupts a child's brain development and information processing, increasing the likelihood that the youngster may experience mental health issues in the future [88]. Research indicates that children with a history of parental divorce are 1.66 times more likely to experience mental health issues in their later years [51, 89]. Research indicates that children with a history of parental divorce are 1.66 times more likely to experience mental health issues in their later years [90].

Generally, this umbrella review underscores the global impact of ACEs on mental health. The inclusion of SRM research encompassing a diverse range of populations from various cultural, ethnic, and socioeconomic backgrounds can uncover how ACEs manifest and influence mental health outcomes in a view of a global context. However, future research should welcome to prioritize a more nuanced understanding of the ACE-mental health relationship and inform culturally sensitive prevention and intervention strategies [91]. Additionally, confounding variables like socioeconomic status, genetics, and environmental factors should be considered as crucial factors for developing mental health problems to develop comprehensive prevention and intervention strategies [92].

Strengths and Limitations of the Study

The study covers many data sources including many systematic reviews and meta-analyses, providing a comprehensive view of the association between ACEs and mental health problems later in life. The research methodology follows PRISMA guidelines and is robust, ensuring that the included studies meet specific criteria for quality and relevance. The AMSTAR tool is appropriately used for quality assessment. Subgroup analyses by economic classification are conducted, enhancing the study's depth. Despite these strengths, the study also has a few limitations: as the included studies were not from all

Fig. 4. Forest plot shows subgroup analysis of the pooled effect of ACE on the development of mental health problems later in life by type of ACE in a global context.

countries and this may affect the generalizability of the pooled result. This study's results also with a high level of heterogeneity despite the authors' trying to reduce it by using a weighted inverse variance random-effects model to pool the results and subgroup analysis.

Conclusions and Recommendations

This umbrella review revealed that ACEs have a statistically significant association (with 66% increased risk) with anxiety and depression later in life in a global context. The odds of developing mental health problems later in life were 4.13, 1.5, 1.56, 2.07, 5.55, 1.73, 2.11, and 1.66 times higher among individuals with a history of domestic violence, maltreatment, physical abuse, sexual abuse, child abuse, parental mental health problems, neglect, and parental divorce, respectively. It appears that childhood periods are a critical window of opportunity for reducing the risk of developing mental illness in the future and for implementing intervention measures. Preventing childhood maltreatment and addressing psychiatric risk factors can prevent psychopathology. Longitudinal and interventional studies are needed to optimize healthcare responses to ACEs. Increased awareness and public health interventions are needed to prevent childhood adversity and prevent mental problems among these victims.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding Sources

There was no funding source for this study.

Author Contributions

B.B.A. conceived the study. B.B.A., A.K.S., A.M., G.K.A., M.A., A.W.A., A.B.Z., T.A.K., A.K., T.W., A.M.K., G.Y., and M.A.K. designed and wrote the draft of the manuscript. All authors critically reviewed the manuscript for important intellectual content and contributed to the final approval of the version to be submitted.

Data Availability Statement

The data used in the analysis of this study is available in the manuscript. Further inquiries can be directed to the corresponding author.

References

1 Sahle BW, Reavley NJ, Li W, Morgan AJ, Yap MBH, Reupert A, et al. The association between adverse childhood experiences and common mental disorders and suicidality: an umbrella review of systematic reviews and meta-analyses. Eur Child Adolesc Psychiatry. 2022;31(10):1489–99. https://doi.org/10.1007/s00787-021-01745-2

2 Trevillion K, Oram S, Feder G, Howard LM. Experiences of domestic violence and mental disorders: a systematic review and meta-analysis. PLoS One. 2012;7(12):e51740. https://doi.org/10.1371/journal.pone.0051740

3 Jones TM, Nurius P, Song C, Fleming CM. Modeling life course pathways from adverse childhood experiences to adult mental health. Child Abuse Negl. 2018;80:32–40. https://doi.org/10.1016/j.chiabu.2018.03.005

4 Fujiwara T. Impact of adverse childhood experience on physical and mental health: a life-course epidemiology perspective. Psychiatry Clin Neurosci. 2022;76(11):544–51. https://doi.org/10.1111/pcn.13464

5 Li M, D'Arcy C, Meng X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. Psychol Med. 2016;46(4):717–30. https://doi.org/10.1017/S0033291715002743

6 Taillieu TL, Brownridge DA, Sareen J, Afifi TO. Childhood emotional maltreatment and mental disorders: results from a nationally representative adult sample from the United States. Child Abuse Negl. 2016;59:1–12. https://doi.org/10.1016/j.chiabu.2016.07.005

7 Cicchetti D, Toth SL. Child maltreatment and developmental psychopathology: a multilevel perspective. Developmental psychopathology. 2016;3:457–512.

8 Toth SL, Cicchetti D. The impact of relatedness with mother on school functioning in maltreated children. J Sch Psychol. 1996;34(3):247–66. https://doi.org/10.1016/0022-4405(96)00014-3

9 Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA. The global burden of anxiety disorders in 2010. Psychol Med. 2014;44(11):2363–74. https://doi.org/10.1017/S0033291713003243

10 Salleh MR. The burden of mental illness: an emerging global disaster. J Clin Health Sci. 2018;3(1):5–8. https://doi.org/10.24191/jchs.v3i1.6150

11 US Burden of Disease Collaborators; Mokdad AH, Ballestros K, Echko M, Glenn S, Olsen HE, et al. The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. JAMA. 2018;319(14):1444–72. https://doi.org/10.1001/jama.2018.0158

12 Agnafors S, Torgerson J, Rusner M, Kjellström AN. Injuries in children and adolescents with psychiatric disorders. BMC public health. 2020;20(1):1273–10. https://doi.org/10.1186/s12889-020-09283-3

13 Baiden P, Stewart SL, Fallon B. The role of adverse childhood experiences as determinants of non-suicidal self-injury among children and adolescents referred to community and inpatient mental health settings. Child Abuse Negl. 2017;69:163–76. https://doi.org/10.1016/j.chiabu.2017.04.011

14 Cecil CA, Viding E, Fearon P, Glaser D, McCrory EJ. Disentangling the mental health impact of childhood abuse and neglect. Child Abuse Negl. 2017;63:106–19. https://doi.org/10.1016/j.chiabu.2016.11.024
15 Tanaka M, Wekerle C, Schmuck ML, Paglia-Boak A; MAP Research Team. The linkages among childhood maltreatment, adolescent mental health, and self-compassion in child welfare adolescents. Child Abuse Negl. 2011;35(10):887–98. https://doi.org/10.1016/j.chiabu.2011.07.003
16 Martin J, Taylor MJ, Lichtenstein P. Assessing the evidence for shared genetic risks across psychiatric disorders and traits. Psychol Med. 2018;48(11):1759–74. https://doi.org/10.1017/S0033291717003440
17 McAdams TA, Neiderhiser JM, Rijsdijk FV, Narusyte J, Lichtenstein P, Eley TC. Accounting for genetic and environmental confounds in associations between parent and child characteristics: a systematic review of children-of-twins studies. Psychol Bull. 2014;140(4):1138–73. https://doi.org/10.1037/a0036416
18 Dube SR, Cook ML, Edwards VJ. Peer reviewed: health-related outcomes of adverse childhood experiences in Texas, 2002. Prev Chronic Dis. 2010;7(3):A52.
19 Chartier MJ, Walker JR, Naimark B. Separate and cumulative effects of adverse childhood experiences in predicting adult health and health care utilization. Child Abuse Negl. 2010;34(6):454–64. https://doi.org/10.1016/j.chiabu.2009.09.020
20 Mc Elroy S, Hevey D. Relationship between adverse early experiences, stressors, psychosocial resources and wellbeing. Child Abuse Negl. 2014;38(1):65–75. https://doi.org/10.1016/j.chiabu.2013.07.017
21 Shonkoff JP, et al. *Excessive stress disrupts the architecture of the developing brain. National Scientific Council on the Developing Child*. Working Paper; 2005. Vol. Vol. 3; p. 2014.
22 Mersky JP, Topitzes J, Reynolds A. Impacts of adverse childhood experiences on health, mental health, and substance use in early adulthood: a cohort study of an urban, minority sample in the US. Child Abuse Negl. 2013;37(11):917–25. https://doi.org/10.1016/j.chiabu.2013.07.011
23 Piatt EE, Munetz MR, Ritter C. An examination of premature mortality among decedents with serious mental illness and those in the general population. Psychiatr Serv. 2010;61(7):663–8. https://doi.org/10.1176/ps.2010.61.7.663
24 Bhattarai A, Dimitropoulos G, Marriott B, Paget J, Bulloch AGM, Tough SC, et al. Can the Adverse Childhood Experiences (ACEs) checklist be utilized to predict emergency department visits among children and adolescents? BMC Med Res Methodol. 2021;21:195–16. https://doi.org/10.1186/s12874-021-01392-w
25 Chitnis A, Amoloja T, Vanderkarr M, Folly E, Sparks C, Holy C. PIT15 complications, health resource utilization and costs associated with hardware removal within 1-YEAR after open reduction internal fixation of humerus fractures. Value in Health. 2019;22:S213–4. https://doi.org/10.1016/j.jval.2019.04.987
26 Majid M, Ab Rahman A, Taib F. Adverse childhood experiences and health risk behaviours among the undergraduate health campus students. Malays J Med Sci. 2023;30(1):152–61. https://doi.org/10.21315/mjms2023.30.1.13
27 Jones AC, Badour CL, Alex Brake C, Hood CO, Feldner MT. Facets of emotion regulation and posttraumatic stress: an indirect effect via peritraumatic dissociation. Cognit Ther Res. 2018;42(4):497–509. https://doi.org/10.1007/s10608-018-9899-4
28 Melara RD, Ruglass LM, Fertuck EA, Hien DA. Regulation of threat in post-traumatic stress disorder: associations between inhibitory control and dissociative symptoms. Biol Psychol. 2018;133:89–98. https://doi.org/10.1016/j.biopsycho.2018.01.017
29 Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc. 2015;13(3):132–40. https://doi.org/10.1097/XEB.0000000000000055
30 Abate BB, Tilahun BD, Yayeh BM. Global COVID-19 vaccine acceptance level and its determinants: an umbrella review. BMC Public Health. 2024;24(1):5. https://doi.org/10.1186/s12889-023-17497-4
31 Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7(1):10–7. https://doi.org/10.1186/1471-2288-7-10
32 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58. https://doi.org/10.1002/sim.1186
33 Abate BB, Kassie AM, Kassaw MW, Aragie TG, Masresha SA. Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis. BMJ open. 2020;10(10):e040129. https://doi.org/10.1136/bmjopen-2020-040129
34 Baldwin JR, Wang B, Karwatowska L, Schoeler T, Tsaligopoulou A, Munafò MR, et al. Childhood maltreatment and mental health problems: a systematic review and meta-analysis of quasi-experimental studies. Am J Psychiatry. 2023;180(2):117–26. https://doi.org/10.1176/appi.ajp.20220174
35 Racine N, Deneault AA, Thiemann R, Turgeon J, Zhu J, Cooke J, et al. Intergenerational transmission of parent adverse childhood experiences to child outcomes: a systematic review and meta-analysis. Child Abuse Negl. 2023:106479. https://doi.org/10.1016/j.chiabu.2023.106479
36 Gallo EAG, Munhoz TN, Loret de Mola C, Murray J. Gender differences in the effects of childhood maltreatment on adult depression and anxiety: a systematic review and meta-analysis. Child Abuse Negl. 2018;79:107–14. https://doi.org/10.1016/j.chiabu.2018.01.003
37 Jonas L, Salazar de Pablo G, Shum M, Nosarti C, Abbott C, Vaquerizo-Serrano J. A systematic review and meta-analysis investigating the impact of childhood adversities on the mental health of LGBT+ youth. JCPP Adv. 2022;2(2):e12079. https://doi.org/10.1002/jcv2.12079
38 Mitiku KW, Tegegne E, Amsalu M, Habtegiorgis SD, Melaku B. Mental illness in children and its determinants in Ethiopia: a systematic review and meta-analysis, 2023. Clin Child Psychol Psychiatr. 2024;29(1):168–86. https://doi.org/10.1177/13591045231209078
39 Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health. 2017;2(8):e356–66. https://doi.org/10.1016/S2468-2667(17)30118-4
40 Lindert J, von Ehrenstein OS, Grashow R, Gal G, Braehler E, Weisskopf MG. Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: systematic review and meta-analysis. Int J Public Health. 2014;59(2):359–72. https://doi.org/10.1007/s00038-013-0519-5
41 Xiao Z, Baldwin MM, Meinck F, Obsuth I, Murray AL. The impact of childhood psychological maltreatment on mental health outcomes in adulthood: a protocol for a systematic review and meta-analysis. Syst Rev. 2021;10(1):224–7. https://doi.org/10.1186/s13643-021-01777-4
42 Ayano G, Betts K, Maravilla JC, Alati R. The risk of anxiety disorders in children of parents with severe psychiatric disorders: a systematic review and meta-analysis. J Affect Disord. 2021;282:472–87. https://doi.org/10.1016/j.jad.2020.12.134
43 McKay MT, Cannon M, Chambers D, Conroy RM, Coughlan H, Dodd P, et al. Childhood trauma and adult mental disorder: a systematic review and meta-analysis of longitudinal cohort studies. Acta Psychiatr Scand. 2021;143(3):189–205. https://doi.org/10.1111/acps.13268
44 Racine N, Devereaux C, Cooke JE, Eirich R, Zhu J, Madigan S. Adverse childhood experiences and maternal anxiety and depression: a meta-analysis. BMC psychiatry. 2021;21(1):28–10. https://doi.org/10.1186/s12888-020-03017-w
45 Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull. 2012;38(4):661–71. https://doi.org/10.1093/schbul/sbs050

46 Ttofi MM, Farrington DP, Lösel F, Loeber R. Do the victims of school bullies tend to become depressed later in life? A systematic review and meta-analysis of longitudinal studies. J Aggress Confl Peace Res. 2011;3(2):63–73. https://doi.org/10.1108/17596591111132873
47 Lawrence PJ, Murayama K, Creswell C. Systematic review and meta-analysis: anxiety and depressive disorders in offspring of parents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2019;58(1):46–60. https://doi.org/10.1016/j.jaac.2018.07.898
48 Agnew-Blais J, Danese A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatr. 2016;3(4):342–9. https://doi.org/10.1016/S2215-0366(15)00544-1
49 Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med. 2012;9(11):e1001349. https://doi.org/10.1371/journal.pmed.1001349
50 Chen LP, Murad MH, Paras ML, ColbensonKM, Sattler AL, Goranson EN, et al. Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis. Mayo Clin Proc. 2010;85(7):618–29. https://doi.org/10.4065/mcp.2009.0583
51 Sands A, Thompson EJ, Gaysina D. Long-term influences of parental divorce on offspring affective disorders: a systematic review and meta-analysis. J Affect Disord. 2017;218:105–14. https://doi.org/10.1016/j.jad.2017.04.015
52 Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97–111. https://doi.org/10.1002/jrsm.12
53 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557
54 Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. J Eval Clin Pract. 2008;14(5):951–7. https://doi.org/10.1111/j.1365-2753.2008.00986.x
55 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34. https://doi.org/10.1136/bmj.315.7109.629
56 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097
57 Daníelsdóttir HB, Aspelund T, Thordardottir EB, Fall K, Fang F, Tómasson G, et al. Adverse childhood experiences and resilience among adult women: a population-based study. Elife. 2022;11:e71770. https://doi.org/10.7554/eLife.71770
58 Herzog JI, Schmahl C. Adverse childhood experiences and the consequences on neurobiological, psychosocial, and somatic conditions across the lifespan. Front Psychiatry. 2018;9:420. https://doi.org/10.3389/fpsyt.2018.00420
59 Zhu Y, Zhang G, Anme T. Adverse childhood experiences, resilience, and emotional problems in young Chinese children. Int J Environ Res Public Health. 2023;20(4):3028. https://doi.org/10.3390/ijerph20043028
60 Hornor G. Resilience. J Pediatr Health Care. 2017;31(3):384–90. https://doi.org/10.1016/j.pedhc.2016.09.005
61 Morgan CA, Chang YH, Choy O, Tsai MC, Hsieh S. Adverse childhood experiences are associated with reduced psychological resilience in youth: a systematic review and meta-analysis. Children. 2021;9(1):27. https://doi.org/10.3390/children9010027
62 Xiao Z, Murat Baldwin M, Wong SC, Obsuth I, Meinck F, Murray AL. The impact of childhood psychological maltreatment on mental health outcomes in adulthood: a systematic review and meta-analysis. Trauma Violence Abuse. 2023;24(5):3049–64. https://doi.org/10.1177/15248380221122816
63 McKay MT, Kilmartin L, Meagher A, Cannon M, Healy C, Clarke MC. A revised and extended systematic review and meta-analysis of the relationship between childhood adversity and adult psychiatric disorder. J Psychiatr Res. 2022;156:268–83. https://doi.org/10.1016/j.jpsychires.2022.10.015
64 Available from: https://theconversation.com/how-chronic-stress-changes-the-brain-and-what-you-can-do-to-reverse-the-damage-133194#:~:text=The%20reduced%20hippocampus%20that%20a%20persistent%20exposure%20to,brain%20which%20modulate%20cognition%20and%20mood%2C%20including%20serotonin
65 Available from: https://www.ncmh.info/2019/08/22/adverse-childhood-experiences-and-the-developing-brain/#:~:text=If%20a%20person%20is%20in%20a%20constant%20state,p.c
66 Hailes HP, Yu R, Danese A, Fazel S. Long-term outcomes of childhood sexual abuse: an umbrella review. Lancet Psychiatr. 2019;6(10):830–9. https://doi.org/10.1016/S2215-0366(19)30286-X
67 Shonkoff JP, Garner AS; Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. Pediatrics. 2012;129(1):e232–46. https://doi.org/10.1542/peds.2011-2663
68 Madigan S, Deneault AA, Racine N, Park J, Thiemann R, Zhu J, et al. Adverse childhood experiences: a meta-analysis of prevalence and moderators among half a million adults in 206 studies. World psychiatry. 2023;22(3):463–71. https://doi.org/10.1002/wps.21122
69 Ontario Agency for Health Protection and Promotion (Public Health Ontario). Carsley S, O.T.I.t.p.a.m.t.i.o.a.c.e.A.i.C.
70 Williams RC. From ACEs to early relational health: implications for clinical practice. Paediatr Child Health. 2023;28(6):377–93. https://doi.org/10.1093/pch/pxad025
71 Doroudchi A, Zarenezhad M, Hosseininezhad H, Malekpour A, Ehsaei Z, Kaboodkhani R, et al. Psychological complications of the children exposed to domestic violence: a systematic review. Egypt J Forensic Sci. 2023;13(1):26. https://doi.org/10.1186/s41935-023-00343-4
72 Wang Q, Wu HT, Liu C, Huang XT, Xu XR, Wu BY. A pathway analysis of the impact of childhood domestic violence on depression in middle-aged and elderly people from the perspective of life course. Child Abuse Negl. 2023;145:106403. https://doi.org/10.1016/j.chiabu.2023.106403
73 Available from: https://www.psychiatry.org/patients-families/domestic-violence#:~:text=Exposure%20to%20traumatic%20events%20can,a.s.t.o.b.t.S.o.d
74 Gardner M, Thomas H, Erskine H. The association between five forms of child maltreatment and depressive and anxiety disorders: a systematic review and meta-analysis. Child Abuse Negl. 2019;96:104082. https://doi.org/10.1016/j.chiabu.2019.104082
75 Humphreys KL, LeMoult J, Wear JG, Piersiak HA, Lee A, Gotlib IH. Child maltreatment and depression: a meta-analysis of studies using the childhood trauma questionnaire. Child Abuse Negl. 2020;102:104361. https://doi.org/10.1016/j.chiabu.2020.104361
76 Strathearn L, Giannotti M, Mills R, Kisely S, Najman J, Abajobir A. Long-term cognitive, psychological, and health outcomes associated with child abuse and neglect. Pediatrics. 2020;146(4):e20200438. https://doi.org/10.1542/peds.2020-0438
77 Kaufman J. Child abuse and psychiatric illness. Biol Psychiatry. 2012;71(4):280–1. https://doi.org/10.1016/j.biopsych.2011.12.006
78 Dworkin ER. Risk for mental disorders associated with sexual assault: a meta-analysis. Trauma Violence Abuse. 2020;21(5):1011–28. https://doi.org/10.1177/1524838018813198
79 Available from: https://theconversation.com/people-who-experience-childhood-sexual-abuse-tell-us-it-affects-their-entire-life-and-research-backs-them-up-195452#:~:text=There%20are%20many%20reasons%20why%20people%20who%20experience,from%20a%20learned%20lack%20of%20trust%20in%20others
80 Available from: https://www.goodencenter.org/the-link-between-child-abuse-and-mental-illness/
81 Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. Schizophr Bull. 2014;40(1):28–38. https://doi.org/10.1093/schbul/sbt114

82 Gatt JM, Burton KLO, Williams LM, Schofield PR. Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. J Psychiatr Res. 2015;60:1–13. https://doi.org/10.1016/j.jpsychires.2014.09.014
83 Available from: https://www.amenclinics.com/blog/5-ways-your-family-history-affects-your-mental-health/
84 Moore SE, Norman RE, Suetani S, Thomas HJ, Sly PD, Scott JG. Consequences of bullying victimization in childhood and adolescence: a systematic review and meta-analysis. World J Psychiatry. 2017;7(1):60–76. https://doi.org/10.5498/wjp.v7.i1.60
85 Zaen NA, Nuha RU, Veibiani NA. Meta analysis: the effect of bullying on adolescents on mental health and depression. J Epidemiol Public Healt. 2022;7(1):104–19. https://doi.org/10.26911/jepublichealth.2022.07.01.09.
86 Abregú-Crespo R, Garriz-Luis A, Ayora M, Martín-Martínez N, Cavone V, Carrasco MÁ, et al. School bullying in children and adolescents with neurodevelopmental and psychiatric conditions: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2024;8(2):122–34. https://doi.org/10.1016/S2352-4642(23)00289-4
87 Winding TN, Skouenborg LA, Mortensen VL, Andersen JH. Is bullying in adolescence associated with the development of depressive symptoms in adulthood? a longitudinal cohort study. BMC Psychol. 2020;8:122–9. https://doi.org/10.1186/s40359-020-00491-5
88 Available from: https://developingchild.harvard.edu/science/deep-dives/neglect/#:~:text=Studies%20on%20children%20in%20a%20variety%20of%20settings,r.f.a.C.e.C
89 Auersperg F, Vlasak T, Ponocny I, Barth A. Long-term effects of parental divorce on mental health–A meta-analysis. J Psychiatr Res. 2019;119:107–15. https://doi.org/10.1016/j.jpsychires.2019.09.011
90 Schaan VK, Vögele C. Resilience and rejection sensitivity mediate long-term outcomes of parental divorce. Eur Child Adolesc Psychiatry. 2016;25(11):1267–9. https://doi.org/10.1007/s00787-016-0893-7
91 Gopalkrishnan N. Cultural diversity and mental health: considerations for policy and practice. Front Public Health. 2018;6:179. https://doi.org/10.3389/fpubh.2018.00179
92 Badini I, Ahmadzadeh Y, Wechsler DL, Lyngstad TH, Rayner C, Eilertsen EM, et al. Socioeconomic status and risk for child psychopathology: exploring gene–environment interaction in the presence of gene–environment correlation using extended families in the Norwegian Mother, Father and Child Birth Cohort Study. J Child Psychol Psychiatry. 2024;65(2):176–87. https://doi.org/10.1111/jcpp.13872