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Review article

Association between adverse childhood experiences and mortality: A systematic review and meta-analysis

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ABSTRACT

Adverse childhood experiences represent a critical public health concern that warrants urgent attention and cannot be overlooked. The evidence regarding the relationship between adverse childhood experiences and mortality has been insufficient and inconsistent. To address this gap, we conducted a systematic review and meta-analysis to explore the association between adverse childhood experiences, including their subtypes, and various mortality outcomes. We systematically searched PubMed, Web of Science, EMBASE, CINAHL, and the Cochrane Library from inception to 9 March 2024. Ultimately, 49 studies were included. Among them, 46 studies involving 24,276,424 participants investigated the association between adverse childhood experiences and mortality. The results showed adverse childhood experiences were significantly associated with overall mortality (OR, 1.64; 95 % CI, 1.51 to 1.78; P < 0.001), external cause mortality (OR, 1.91; 95 % CI, 1.7 to 2.15; P < 0.001), and internal cause mortality (OR, 1.3; 95 % CI, 1.17 to 1.44; P < 0.001). Among women and men, the effect sizes were 1.39 (95 %CI, 1.25 to 1.54; P < 0.001) and 1.4 (95 %CI, 1.22 to 1.6; P < 0.001), respectively. Increased mortality risk was also observed for those exposed to maltreatment (OR, 1.95; 95 %CI, 1.65 to 2.3; P < 0.001), household dysfunction (OR, 1.36; 95 %CI, 1.22 to 1.51; *P* < 0.001), low socioeconomic status (OR, 1.25; 95 %CI, 1.09 to 1.43; *P* = 0.002), or out-of-home care (OR, 2.87; 95 %CI, 2.12 to 3.9; *P* < 0.001). Gender differences were not statistically significant, except for minor variations within the low socioeconomic status. This study underscores the profound impact of adverse childhood experiences on mortality risk, highlighting the need for targeted public health interventions and policies.

1. Introduction

1.1. The concept of adverse childhood experiences

Adverse childhood experiences (ACEs) refer to a wide range of traumatic events (e.g., child maltreatment or household dysfunction) that occur during childhood (0–17 years) (National Center for Injury Prevention and Control, 2023). Child maltreatment includes physical, emotional, or sexual abuse, as well as neglect, deprivation, or commercial or other exploitation that impairs a child's development and survival. Household dysfunction indirectly affects children through the

family environment, including factors such as parental separation, substance abuse, incarceration, prolonged unemployment, severe somatic or mental illness, and the death of a parent or a sibling (Andersen, 2021; Clemens et al., 2019; Rod et al., 2023). As research in this field progresses, the concept of adverse childhood experiences continues to expand, encompassing a wider range of factors (e.g., violence outside the family, low socioeconomic status, or involvement with child welfare services) (Finkelhor et al., 2013; Jackisch et al., 2019). Involvement with child welfare services encompasses both out-of-home care and in-home services.

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1.2. Global burden of ACEs

Adverse childhood experiences are common globally. A recent metaanalysis summarizing 206 studies showed that the prevalence of experiencing one adverse childhood experience was 22.4 %, and the prevalence was 16.1 % for experiencing four or more adverse childhood experiences (Madigan et al., 2023). The health-related economic costs due to adverse childhood experiences are substantial, with estimated annual costs of \$581 billion in Europe and \$748 billion in North America (Bellis et al., 2019). The high prevalence of adverse childhood experiences, along with their negative impacts, represents a significant public health issue. Healthcare systems are actively working to design and implement comprehensive public health strategies and intervention programs to mitigate their impact (Oral et al., 2016).

1.3. The impacts of ACEs on health

Evidence indicates that early childhood development could negatively affect lifelong health and well-being (Shonkoff et al., 2012). Epidemiological and neurobiological studies indicate that adverse childhood experiences could act as toxic stressors, affecting brain structure and function, as well as endocrine, immune, and metabolic systems (Shonkoff et al., 2012; Berens et al., 2017; Herzog and Schmahl, 2018). These processes ultimately lead to adverse effects on learning, behavior, and health. Previous systematic reviews have found that adverse childhood experiences are associated with a range of health outcomes, including cancer, cardiovascular diseases, diabetes, obesity, anxiety, depression, sleep disorders, and mental disorders (Felitti et al., 1998; Norman et al., 2012; Huang et al., 2015; Holman et al., 2016; Hughes et al., 2017; Bellis et al., 2019; Schroeder et al., 2021; Yu et al., 2022).

1.4. The link between ACEs and mortality

Studies investigating the association between adverse childhood experiences and mortality have yielded inconsistent conclusions. While some studies have revealed a significant correlation (Johnson et al., 2020; Puterman et al., 2020; Rod et al., 2020), others have reported no significant association (Ferguson et al., 2017; Steel et al., 2020; White and Widom, 2003). This might be attributed to variations in study design (prospective or retrospective, length of follow-up), differences in covariate adjustments, and population characteristics (patients or general population). Clarifying the factors contributing to these inconsistencies requires further research. According to a meta-analysis, specific types including physical, emotional, and sexual abuse were not found to be statistically significantly associated with a high risk of mortality (D'arcy-Bewick et al., 2022). However, among women, both physical and emotional abuse were found to be associated with an increased risk of mortality. Another meta-analysis encompassing six cohort studies revealed a significant association between adverse childhood experiences and mortality (Ahmadi et al., 2016). However, the number of articles included was small, and the relationship between subtypes and mortality was not analyzed. Different types of adverse childhood experiences exhibit varying contributions to mortality outcomes (Johnson et al., 2020; Rogers et al., 2021; Bhattarai et al., 2023). Moreover, some research has suggested that women who have experienced adverse childhood experiences might face a higher risk of mortality compared to men (Chen et al., 2016; Lee and Ryff, 2019). In recent years, the body of research exploring the associations between adverse childhood experiences and various mortality outcomes has grown extensively (Rod et al., 2020; Morton et al., 2021; Wang et al., 2023). Given the divergent evidence, inadequacy of previous systematic reviews, and availability of novel data, it is imperative to conduct a systematic review and meta-analysis to examine the association of adverse childhood experiences and mortality.

1.5. Aim of the study

This study aims to: (1) examine the association between adverse childhood experiences and mortality; (2) explore the relationship between subtypes of adverse childhood experiences and mortality; (3) analyze gender disparities in the association between adverse childhood experiences and mortality; (4) examine the association between adverse childhood experiences and specific mortality outcomes (e.g., suicide, cancer, or external causes).

2. Methods

Our paper followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) for reporting the findings. The protocol was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO) by the National Institute for Health Research (NIHR) (Protocol registration ID: CRD42023489159).

2.1. Search strategy

Five electronic databases were searched with no time restrictions (from the inception to 9 March 2024): PubMed, Web of Science, EMBASE, CINAHL, and the Cochrane Library. The literature search used terms related to adverse childhood experiences and mortality with a combination of Medical Subject Headings (MeSH) words and entry terms. For example, in PubMed, we employed MeSH terms such as "mortality," "death," "survival," and "Adverse Childhood Experiences." No filters were applied to ensure comprehensive retrieval of relevant literature. We also manually conducted a cross-reference search of all relevant articles and other reviews for potentially eligible articles. Detailed information on search strategies is presented in Appendix 1.

2.2. Eligibility criteria

The review examined the association between adverse childhood experiences and mortality risk. The inclusion criteria were as follows: (1) exposure of interest: adverse childhood experiences documented through valid measures or formal records; (2) comparison: individuals without adverse childhood experiences; (3) the primary outcome was mortality, and studies needed to report effect sizes using odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with corresponding 95 % confidence intervals (CIs), or provide sufficient data to calculate effect sizes; (4) study design: retrospective or prospective cohort studies published in English. Conference abstracts, editorials, protocols, letters, comments, reviews, and articles without full text were excluded.

2.3. Study selection and data extraction

Two independent authors (LZ and GL) initially screened the titles and abstracts of the retrieved records. Next, they assessed the full texts of potentially eligible articles based on the eligibility criteria. Discrepancies were resolved through discussion, with a third senior investigator (LC) serving as an arbitrator when necessary. Data extraction was performed independently by two researchers (LZ and GL) using a preliminary extraction form. Extracted data encompassed author, publication year, location, sample size, population, age at recruitment, duration of followup, type of adverse childhood experiences, outcome events, effect size from the most adjusted regression model, and adjusted covariates. When both crude and multivariable-adjusted effect estimates were reported, the most fully adjusted outcomes were extracted for analysis.

2.4. Statistical methods

Relative risks (RRs), hazard ratios (HRs), and odds ratios (ORs) were transformed into natural log formats to address skewness and were used to calculate pooled effect sizes for the relationship between adverse childhood experiences and mortality. Heterogeneity was assessed with I^2 statistic and Cochran's Q test (significant when P < 0.10). When substantial heterogeneity was detected, indicated by $I^2 \ge 50$ %, the DerSimonian and Laird random-effects model was used to account for between-study variability. Otherwise, the inverse-variance fixed effects model was used, assuming that the included studies shared a common effect size. Publication bias was examined through visual inspection of the funnel plot and Egger's test (significant when P < 0.05). If publication bias was detected, the trim-and-fill method was used to adjust the influence of bias. Subgroup analyses involved the following categorical variables: type of adverse childhood experiences (maltreatment versus household dysfunction versus other types), gender (women versus men), population (patients with trauma versus general), and mortality outcome (all-cause mortality versus cause-specific mortality). To ensure the robustness of our results, we conducted leave-one-out analyses as sensitivity analyses to explore the impact of each study on the overall results. All statistical analyses were performed using Stata Version 18.0, with alpha set at 0.05, two-tailed.

2.5. Appraisal of methodology and evidence

The Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality of eligible studies (Stang, 2010). This tool evaluates studies across three domains with a total of 9 points: selection, comparability, and outcome assessment. Scores from 0 to 3, 4 to 6, and 7 to 9 indicate low, moderate, and high quality, respectively. The quality of evidence was determined using the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) approach in GRADEpro (Guyatt et al., 2008). The evidence was categorized into four levels of certainty: high, moderate, low, and very low.

3. Results

3.1. Search results

Fig. 1 shows the search process and results. A total of 13,081 articles were retrieved, of which 69 were retained after deduplication and reviewing titles and abstracts. The retained plus additional 16 records from reference lists and other reviews were for full-text screening. Ultimately, 49 studies were included (Alm et al., 2019; Babl et al., 2020; Bhattarai et al., 2023; Björkenstam et al., 2017; Brännström et al., 2020; Brown et al., 2009, 2010; Campbell et al., 2019; Chandan et al., 2020; D'Arcy-Bewick et al., 2023; Deans et al., 2013; Delaplain et al., 2021; Ferguson et al., 2017; Friedman et al., 2012; Geoffroy et al., 2023; Gilard-Pioc et al., 2019; Hanson et al., 2023; Hjern et al., 2004; Huang et al., 2022; Jackisch et al., 2019; Jackisch and Almquist, 2023; Johnson et al., 2020; Juon et al., 2003; Kelly-Irving, Lepage, et al., 2013; Larson and Halfon, 2013; Lee and Rvff, 2019; Lee and White, 2012; Livingston et al., 2019; Morton et al., 2021; Puterman et al., 2020; Putnam-Hornstein, 2011; Putnam-Hornstein et al., 2014; Roaten et al., 2006; Rod et al., 2020, 2023; Rogers et al., 2021; Sabotta and Davis, 1992; Schneiderman et al., 2021; Segal et al., 2021; Sills et al., 2005; Smith et al., 1998; Steel et al., 2020; Theodorou et al., 2021; Wang et al., 2023; Weitoft et al., 2003; White and Widom, 2003; Yock-Corrales et al., 2024; Yu et al., 2017).



Fig. 1. Flow chart of the study selection process for this review.

3.2. Description of the included studies

The characteristics of the included studies are provided in Appendix 2. The publication years ranged from 1992 to 2024, with a majority published in 2019 and later (n = 28, 57 %). Geographically, studies were conducted in North America (n = 28), Latin America (n = 1), Europe (n= 19), and Asia Pacific (n = 5). Sample sizes varied from 190 to 5005,029. Participant ages at recruitment ranged from <1 week to 86 years. The sample population encompassed the general population (n =34), patients with trauma (n = 11), cancer patients (n = 1) (Steel et al., 2020), female nurses (n = 1) (Wang et al., 2023), Seventh-day Adventists (n = 1) (Morton et al., 2021), and poor people (n = 1) (Juon et al., 2003). The follow-up duration ranged from 0.8 to 54 years. Types of adverse childhood experiences measured in the included studies included maltreatment (physical abuse, sexual abuse, emotional abuse, mental abuse, neglect, n = 35), household dysfunction (single parent, parental substance abuse, prolonged parental unemployment, adverse family structure, serious conflict at home, major upheaval between parents, parental mental illness, substantial parental criminality or incarceration, death or suicide in the family, poor family relationships, residential instability, n = 19), involvement with child welfare services (out-of-home care, in-home services, n = 10), low socioeconomic status (n = 9), poor health (n = 4), bullying (n = 1), war and natural disaster (n = 1)= 1), had to repeat a year of school (n = 1), victim of violence (n = 1), witnessing abuse (n = 1), prolonged trauma (n = 1), and household receiving public assistance (n = 1). The outcome events encompassed internal cause mortality (e.g., COVID-19-related death, cancer, disease mortality), external cause mortality (e.g., suicide, injury, accidents, homicide), and all-cause mortality. Among six studies, no covariate adjustment was performed in data analyses.

The results of the quality assessment are summarized in Appendix 3. The quality score ranged from 5 to 9 scores. Based on the Newcastle–Ottawa scale, 15 articles were classified as medium quality, while 34 articles were rated as high quality.

3.3. Meta-analysis

3.3.1. All adversity childhood experiences and mortality

Table 1 presents the effect sizes for different groups based on predefined variables. A comprehensive analysis of 46 studies, including 24,276,424 individuals, examined the association between adverse childhood experiences and mortality. The remaining three articles (Brown et al., 2010; Jackisch and Almquist, 2023; Lee and Ryff, 2019), while included in the dataset of the initial 46, provided essential detailed information for subgroup analysis. The overall pooled effect estimate from the 46 studies was an OR of 1.64 (95 %CI, 1.51 to 1.78; *P* < 0.001) (Fig. 2). Appendix 5 presents the remaining forest plots. Notably, substantial heterogeneity was observed among the studies (I^2 =95.7 %, P <0.001), leading to the conduction of subgroup analyses. The funnel plot and Egger's test (P < 0.001) indicated statistically significant publication bias (Fig. 3). However, the trim-and-fill analysis suggested that there were no potential missing studies to adjust for publication bias. For women and men, the pooled effect estimates were 1.39 (95 %CI, 1.25 to 1.54; P < 0.001; $I^2 = 78.7$ %; P < 0.001) and 1.4 (95 % CI, 1.22 to 1.6; P < 0.001) 0.001; $I^2 = 78.1$ %; P < 0.001), respectively. Egger's test (P = 0.021) revealed potential publication bias in studies on women, yet trim-and-fill analysis suggested consistency, indicating no need for additional studies. Thirteen studies explored the impact of adverse childhood experiences on external cause mortality (OR, 1.91; 95 % CI, 1.7 to 2.15; P < 0.001; $I^2 = 82.5$ %; P < 0.001), while 12 studies explored internal cause mortality (OR, 1.3; 95 % CI, 1.17 to 1.44; P < 0.001; I^2 =78.1 %; P < 0.001). A pooled estimate from seven studies showed adverse childhood experiences were associated with a higher risk of suicide mortality (OR, 1.89; 95 % CI, 1.61 to 2.22; P < 0.001; $I^2 = 78.5$ %; P < 0.001). Additionally, a summary of 11 articles based on patients with trauma demonstrated a significant association between adverse

childhood experiences and mortality (OR, 3.52; 95 %CI, 2.05 to 6.03; *P* < 0.001; I^2 =95.1 %; *P* < 0.001). A meta-analysis of 17 studies suggested that adverse childhood experiences occurring before age 13 were significantly associated with higher mortality (OR, 2.16; 95 %CI, 1.70 to 2.74; *P* < 0.001; I^2 =91.3 %; *P* < 0.001).

Meta-regression analysis was conducted to identify the causes of heterogeneity (Appendix 4). Results showed that heterogeneity was not related to gender or geographic region. Significant factors contributing to heterogeneity included follow-up duration, population characteristics, study design, adjustments for covariates, and assessment methods for adverse childhood experiences.

3.3.2. Maltreatment and mortality

A total of 27 articles, including 14,015,735 individuals, assessed the association of maltreatment and mortality. The pooled effect size vielded a significant value of 1.95 (95 % CI, 1.65 to 2.3; P < 0.001; $I^2 = 96.6$ %; P < 0.001). The Egger's test showed statistically significant funnel plot asymmetry (P < 0.001) (Fig. 4), indicating potential bias. The trimand-fill analysis revealed that no additional studies were included to alter the effects. Among these studies, the association of physical abuse and sexual abuse with mortality was investigated in 11 and 3 studies, respectively. Those who experienced physical abuse had a higher risk of mortality (OR, 1.85; 95 % CI, 1.36 to 2.51; P < 0.001; $I^2 = 97.3$ %; P < 0.0010.001), as did those who experienced sexual abuse (OR, 1.4; 95 % CI, 1.06 to 1.83; P = 0.016; $I^2 = 88.2$ %; P < 0.001). Positive associations were also observed for both women (OR, 1.27; 95 % CI, 1.12 to 1.43; P < 0.001; $I^2 = 74.6$ %; P < 0.001) and men (OR, 1.28; 95 % CI, 1.03 to 1.59; P = 0.001; $I^2 = 65.9$ %; P = 0.024). Additionally, maltreatment was also associated with increased external cause mortality (OR, 1.74; 95 % CI, 1.33 to 2.29; P < 0.001; $I^2 = 69.2$ %; P < 0.001) and internal cause mortality (OR, 1.23; 95 % CI, 1.07 to 1.4; P = 0.003; $I^2 = 71.3$ %; P < 10000.001).

3.3.3. Household dysfunction and mortality

A pooled estimate of 13 studies (8878,390 participants) showed household dysfunction was associated with a higher risk of mortality (OR, 1.36; 95 % CI, 1.22 to 1.51; P < 0.001; $I^2 = 85.7$ %; P < 0.001). Six studies revealed a significant impact of single parent on mortality (OR, 1.21; 95 % CI, 1.08 to 1.37; P = 0.001; $I^2 = 66.6$ %; P = 0.002), and four studies reported the influence of death of a family member on mortality (OR, 1.5; 95 % CI, 1.11 to 2.01; P = 0.007; $I^2 = 93.5$ %; P < 0.001). Parental substance abuse was also significantly associated with mortality (OR, 1.39; 95 % CI, 1.03 to 1.88; P = 0.03; $I^2 = 73.2$ %; P = 0.011) based on the meta-analysis of four studies. Four, three, and three studies respectively explored the association between household dysfunction and external cause mortality, internal cause mortality, and suicide. Pooled effect estimates revealed significant associations, with respective values of 1.88 (95 % CI, 1.64 to 2.16; P < 0.001; $I^2 = 64.6$ %; P < 0.001) for external cause mortality, 1.72 (95 % CI, 1.61 to 1.84; *P* < 0.001; I^2 =18.9 %; P = 0.296) for internal cause mortality, and 1.79 (95 % CI, 1.63 to 1.97; P < 0.001; I^2 =40.6 %; P = 0.087) for suicide mortality.

3.3.4. Other types of adverse childhood experiences and mortality

Low socioeconomic status and out-of-home care were investigated in eight and seven studies, respectively, regarding their association with mortality. Significant associations were found between low socioeconomic status (OR, 1.25; 95 % CI, 1.09 to 1.43; P = 0.002; $I^2 = 89.1$ %; P < 0.001), as well as out-of-home care (OR, 2.87; 95 % CI, 2.12 to 3.9; P < 0.001; $I^2 = 78.4$ %; P < 0.001), and mortality. A total of 4 and 3 studies investigated the relationship between low socioeconomic status and mortality among men and women, respectively. The association remained significant in men (OR, 1.23; 95 % CI, 1.10 to 1.37; P < 0.001; $I^2 = 40.5$ %; P = 0.151), whereas no significant relationship was found in women (OR, 1.21; 95 % CI, 0.82 to 1.77; P = 0.339; $I^2 = 79.6$ %; P = 0.002).

Table 1 The pooled effect estimates and certainty of evidence for adverse childhood experiences and mortality.

	No. of studies	ES (95 %CI)	P (Cochron's O)	$P_{\rm ES}$	<i>I</i> ² (%)	P (Eggor's tost)	GRADE Certainty of evidence
			(Cociliali S Q)			(Egger S test)	
ACEs and mortality	46	1.64(1.51, 1.78)	<0.001	<0.001	95.7	<0.001	\bigcirc Very low Downgraded due to inconsistency ^a and publication bias
ACEs and mortality in women	11	1.39(1.25, 1.54)	<0.001	<0.001	78.7	0.021	$\bigcirc \bigcirc \bigcirc$ Very low
ACEs and mortality in men	11	1.4(1.22, 1.6)	<0.001	< 0.001	78.1	0.926	
ACEs and external cause mortality	13	1.91(1.7, 2.15)	<0.001	<0.001	82.5	0.984	Downgraded due to inconsistency" $\bigoplus \bigoplus \bigcup Low$ Downgraded due to inconsistency ^a
ACEs and internal cause mortality	12	1.3(1.17, 1.44)	<0.001	<0.001	78.1	0.716	$\oplus \oplus \bigcirc \bigcirc \text{Low}$ Downgraded due to inconsistency ^a
ACEs and suicide mortality	7	1.89(1.61, 2.22)	<0.001	<0.001	78.5	0.282	$\oplus \oplus \bigcirc \bigcirc \bigcirc$ Low Downgraded due to inconsistency ^a
ACEs and mortality in patients with trauma	11	3.52(2.05, 6.03)	<0.001	<0.001	95.1	0.639	$\bigoplus \bigcirc \bigcirc$ Low
ACEs and mortality in children under 13	17	2.16(1.70, 2.74)	<0.001	< 0.001	91.3	0.390	
Maltreatment and mortality	27	1.95(1.65, 2.3)	<0.001	< 0.001	96.6	<0.001	$\oplus \bigcirc \bigcirc \bigcirc$ Very low
Physical abuse	11	1.85(1.36, 2.51)	<0.001	< 0.001	97.3	0.09	Downgraded due to inconsistency" and publication bias $\bigoplus \bigoplus \bigcup \bigcup$
Sexual abuse	3	1.4(1.06, 1.83)	<0.001	0.016	88.2	0.131	
Maltreatment and mortality in women	6	1.27(1.12, 1.43)	<0.001	<0.001	74.6	0.103	\bigcirc
Maltreatment and mortality in men	6	1.28(1.03, 1.59)	0.024	0.001	65.9	0.949	Downgraded due to inconsistency $\bigoplus \bigoplus \bigoplus \bigoplus \bigoplus \bigcup$
Maltreatment and external cause mortality	4	1.74(1.33, 2.29)	< 0.001	< 0.001	69.2	0.078	$\oplus \oplus \bigcirc \bigcirc$ Low
Maltreatment and internal cause mortality	5	1.23(1.07, 1.4)	<0.001	0.003	71.3	0.422	$\oplus \oplus \bigcirc \bigcirc \text{Low}$ Downgraded due to inconsistency ^a
HD and mortality	13	1.36(1.22, 1.51)	<0.001	<0.001	85.7	0.568	$\oplus \oplus \bigcirc \bigcirc \bigcirc $ Low
Single parent	6	1.21(1.08, 1.37)	0.002	0.001	66.6	0.501	$\oplus \oplus \bigcirc \bigcirc$ Low
Death of family member	4	1.5(1.11, 2.01)	<0.001	0.007	93.5	0.761	$\oplus \oplus \odot$ Low
Parental substance abuse	4	1.39(1.03, 1.88)	0.011	0.03	73.2	0.7	$\oplus \oplus \odot \bigcirc$ Low
HD and external cause mortality	4	1.88(1.64, 2.16)	< 0.001	<0.001	64.6	0.039	$\oplus \oplus \odot$ Low
HD and internal cause mortality	3	1.72(1.61, 1.84)	0.296	< 0.001	18.9	0.231	$ \bigoplus_{n=1}^{\infty} \bigoplus_{i=1}^{\infty} \bigoplus_{j=1}^{\infty} \bigoplus_{j=1}^{\infty} \bigoplus_{j=1}^{\infty} \bigoplus_{i=1}^{\infty} \bigoplus_{j=1}^{\infty} \bigoplus_{i=1}^{\infty} \bigoplus_{j=1}^{\infty} \bigoplus_{i=1}^{\infty} \bigoplus_{j=1}^{\infty} \bigoplus_{i=1}^{\infty} \bigoplus_{j=1}^{\infty} \bigoplus_{i=1}^{\infty} \bigoplus_{j=1}^{\infty} \bigoplus_{$
HD and suicide	3	1.79(1.63, 1.97)	0.087	< 0.001	40.6	0.021	$\oplus \oplus \bigcirc \bigcirc$ Low
Low SES and mortality	8	1.25(1.09, 1.43)	<0.001	0.002	89.1	0.7	$\oplus \oplus \bigcirc \bigcirc Low$
Low SES and mortality in women	3	1.21(0.82, 1.77)	0.002	0.339	79.6	0.25	Downgraded due to inconsistency" $\bigoplus \bigoplus \bigcup Low$ Downgraded due to inconsistency ^a
Low SFS and mortality in men	4	1 23(1 10 1 37)	0 151	<0.001	40.5	0 542	
Out-home-care and mortality	7	2.87(2.12, 3.9)	<0.001	<0.001	78.4	0.966	$\oplus \oplus \bigcirc$ Low Downgraded due to inconsistency ^a

Abbreviations: ES, effect size; HD, household dysfunction; SES, socioeconomic status; ACEs, adverse childhood experiences;. Explanation: a. I square is large (>50 %).

	Study	OR (95% CI)	% Weight
_	Yock-Corrales(2024)	0.72 (0.27, 1.91)	0.44
	Hanson(2023) Rod(2023)-multiple adversity(men)	1.20 (1.06, 1.37) 2.22 (1.32, 3.72)	0.77
	Rod(2023) - persistent deprivation(men)	1.57 (1.15, 2.14)	0.95
	Rod(2023) certy into topTranon(netr) Rod(2023) multiple adversity(women) Rod(2023) Chousehold diversity(women)	1.02(0.52, 2.00) 1.24(0.84, 1.83)	0.64
	Rod(2023) – persistent deprivation(women) Rod(2023) – persistent deprivation(women)	0.82 (0.58, 1.16) 1.01 (0.74, 1.38)	0.92
	Wang(2023)-mild physical abuse Wang(2023)-moderate physical abuse	1.04(0.93, 1.17) 1.11(1.00, 1.22)	1.07 1.08
	Wang(2023)—severe physical abuse Wang(2023)—sexual touching as a child or adolescent	1.42(1.25, 1.61) 0.99(0.90, 1.10)	1.07 1.08
	Wang(2023)—forced sexual activity as a child or adolescent Wang(2023)—forced sexual activity as a child and adolescent	1.11 (0.97, 1.27) 1.64 (1.37, 1.97)	1.06 1.04
	Battarai(2023) – prolonged hospitalization	1.18(0.92, 1.51) 1.18(0.93, 1.51)	1.00
	Bhattarai(2023)-prolonged parental unemployment	1.05 (0.74, 1.50) 1.03 (0.78, 1.37)	0.91
	Bhattarai(2023)-phonged thalma Bhattarai(2023)-phonged labusance use	1.03(0.78, 1.37) 1.03(0.78, 1.37) 1.44(1.03, 2.00)	0.97
	Bhattarai(2023)-being sent away D'Arcy-Bewick(2023)	2.26 (1.43, 3.57) 1.03 (1.01, 1.05)	0.82 1.09
	Huang(2022) Morton(2021)-1 to 3 ACEs	1.00 (0.58, 1.72) 2.51 (1.03, 6.09)	0.75 0.49
	Morton(2021)-4 or more ACEs Delaplain(2021)	2.22 (0.49, 10.03) 2.48 (1.80, 3.41)	0.24 0.94
	Schneiderman(2021) a history of maltreatment report Schneiderman(2021) 2 or more maltreatment reports	1.77 (1.36, 2.30) 3.27 (2.48, 4.30)	0.99
	Rogers(2021)—low socioeconomic status Rogers(2021)—low socioeconomic status	1.93 (1.45, 2.58) 1.43 (1.03, 1.98)	0.97
	Rogers(2021)-physical abuse	1.73 (1.11, 2.71) 0.99 (0.66, 1.47)	0.83 0.87
	Rogers(2021)-witnessing abuse Rogers(2021)-sexual abuse	1.15(0.73, 1.80) 2.64(1.52, 4.59)	0.83 0.74
	Segal(2021)-maltreatment Segal(2021)-out-ol-home care from age 3	2.61 (1.99, 3.43) 4.67 (3.52, 6.20)	0.98 0.97
	Segai(2021) - out-ot-nome care before age 3 Rod(2020) - multiple adversity	1.75 (0.98, 3.14) 4.54 (4.07, 5.06)	0.71
	Rod(2020)-notivential dystituction Rod(2020)-persistent deprivation	1.80 (1.61, 2.00) 1.77 (1.62, 1.93) 1.38 (1.27, 1.51)	1.07
	Johnson(2020) - maltreatment Johnson(2020) - serious e bildhood illness	1.23 (0.93, 1.63) 1.32 (1.00, 1.74)	0.97
	Johnson(2020)—serious conflict at home Johnson(2020)—the overall number of experiences	1.48 (1.12, 1.95) 1.32 (1.03, 1.70)	0.98 1.00
	Puterman(2020) Babl(2020)	1.20 (1.11, 1.31) 105.50 (22.20, 500.40)	1.08 0.23
	Brännström(2020) Chandan(2020)	4.14 (1.61, 10.67) 1.58 (1.27, 1.96)	0.46
	Jackisch(2019)-in-home services	2.41 (1.82, 3.18) 2.91 (2.49, 3.39)	0.59
	Jackisch(2019)-alcohol problems Jackisch(2019)-divorce	1.23(0.99, 1.53) 0.98(0.83, 1.15)	1.02
	Jackisch(2019)-mental illness Jackisch(2019)-incarceration	0.93 (0.77, 1.14) 1.17 (0.85, 1.61)	1.03 0.94
	Jackisch(2019)-death Jackisch(2019)-Tow socioeconomic status	1.15 (0.95, 1.41) 1.03 (0.92, 1.16)	1.03
	Campbell(2019)-ACEs and diabetes Day 2010-ACEs and diabetes	2.32 (1.64, 3.28)	0.97
	Alm(2019) low socioeconomic status Alm(2019) child welfare system	1.47 (1.00, 2.14) 2.59 (1.52, 4.42)	0.89 0.76
	Alm(2019)-parental alcohol abuse	1.84(0.93, 3.66) 0.85(0.44, 1.65)	0.63 0.65
	Livingston(2019) Gilard-Pioc(2019)	13.59 (9.85, 18.77) 10.05 (8.03, 12.58)	0.94
	Björkenstam(2017)—suicide in the family Björkenstam(2017)—suicide Lydetarea abusa	2.90 (1.40, 5.90) 1.90 (1.40, 2.40)	0.89
	Björkenstam(2017)parental psychiatric disorder Björkenstam(2017)parental psychiatric disorder	2.00 (1.50, 2.80) 2.30 (1.70, 3.00)	0.95
	Björkenstam(2017) – single parent Björkenstam(2017) – household receiving public assistance	1.40 (1.20, 1.70) 1.60 (1.30, 2.00)	1.04 1.02
	Björkenstam(2017)-residential instability Yu(2017)	1.60(1.10, 2.40) 1.71(1.57, 1.87)	0.88 1.08
	Putnam-Hornstein(2014)	1.76(0.21, 14.77) 3.22(2.66, 3.89) 1.22(1.00, 1.20)	1.03
	Larson(2013)	1.23(1.09, 1.39) 1.07(0.98, 1.18) 1.06(0.81, 1.39)	1.08
	Kelly–Irving(2013)–2 or more ACEs (men) Kelly–Irving(2013)–1 ACEs (women)	1.57 (1.13, 2.18) 1.66 (1.19, 2.33)	0.94 0.93
	Kelly-Irving(2013)-2 or more ACEs (women) Deans(2013)	1.80 (1.10, 2.95) 2.00 (1.18, 3.38)	0.79 0.76
	Let (2012) Friedman (2012)	2.54 (1.21, 5.34) 2.99 (1.63, 5.45)	0.59
	Putnam-Hornstein(2011) Brown(2009-ACTe score of 6 or more	2.59 (2.27, 2.97)	1.06
	Brown(2009)-ACH: score-1 Brown(2009)-ACH: score-2	0.97 (0.86, 1.10) 1.05 (0.90, 1.23)	1.07 1.05
	Brown(2009)-ACEs score=3 Brown(2009)-ACEs score=4 or 5	0.91(0.73, 1.14) 1.07(0.85, 1.35)	1.01 1.01
	Koaten(2006) Sills(2005)-4-month-olds Sills(2005)-4-month-olds	2.58 (1.84, 3.61) 2.05 (1.22, 3.43) 2.64 (1.20, 4.12)	0.93
	Sills(2005) 43. month olds	4.33 (2.37, 7.89) 2.20 (1.40, 3.60)	0.70
	H]em(2004)-avoidable mortality Weitoft(2003)-men	1.40(0.90, 2.10) 1.21(0.92, 1.59)	0.85
	Weitoft(2003)-women White(2003)	1.54 (1.29, 1.85) 1.17 (0.26, 5.31)	1.04 0.24
	Juon(2003)-mother absent	1.82 (0.93, 3.59) 0.78 (0.10, 6.16) 16 87 (5.10, 55.78)	0.64 0.14 0.34
	Juon(2003)–3 or more residential moves Juon(2003)–5 frequent corporal punishment	1.62(0.84, 3.13) 1.12(0.60, 2.12)	0.65
	Smild(1998) Sabota(1992)	1.19 (1.04, 1.37) 2.90 (2.10, 4.10)	1.06 0.93
	Overall (I-squared = 95.7%, p = 0.000)	1.64 (1.51, 1.78)	100.00
		500	
	.002	200	

Fig. 2. Forest plot of adverse childhood experiences on mortality.



Fig. 3. Funnel plot of adverse childhood experiences on mortality.



Fig. 4. Funnel plot of maltreatment on mortality.

3.4. Sensitivity analysis and certainty of evidence

The sensitivity analysis results indicated that, except for maltreatment in men and sexual abuse, the remaining pooled estimates were robust after excluding each study individually. For maltreatment in men, excluding sequentially two data groups (neglect and physical abuse) from Rogers et al. (2021) and two studies conducted by Putnam-Hornstein et al. (2014) and Sabotta and Davis (1992) rendered the result non-significant. Regarding sexual abuse and mortality, the study by Wang et al. (2023) presented three groups of effect sizes based on the severity of sexual abuse. After sequentially excluding the most serious group and the study of Rogers et al. (2021), the pooled effect size for sexual abuse was no longer significant (Appendix 6). This suggests that the severity of sexual abuse may be a critical factor in its impact. The detailed assessment of evidence is shown in Table 1. Due to observational study designs, substantial heterogeneity, and publication bias, the certainty of evidence was ranked as low (n = 23) or very low (n = 3).

4. Discussion

In this meta-analysis of 49 cohort studies, we found that adverse childhood experiences were significantly associated with mortality, external cause mortality, and internal cause mortality. Whether among men or women, patients or the general population, the relationship remained statistically significant. Subgroup analyses showed maltreatment, household dysfunction, low socioeconomic status, and out-ofhome care were all significantly associated with increased mortality risks. Notably, low socioeconomic status was significantly correlated with increased mortality in men, but not in women. Within the categories of maltreatment and household dysfunction, specific subtypes including physical abuse, sexual abuse, single parent, death of a family member, and parental substance abuse consistently correlated with increased mortality risks.

The results demonstrated diversity in the definitions of adverse childhood experiences. Early research primarily focused on domestic factors such as abuse. As research expanded globally, the significance of external adversities, including peer rejection and community violence, has become increasingly recognized (Alhowaymel et al., 2021; Hartas, 2019). This recognition is particularly evident in populations from specific racial and socioeconomic backgrounds (Cronholm et al., 2015). However, the expanding definitions have raised concerns about potential overlaps with socioeconomic conditions in several studies (Allen and Abresch, 2018; Kelly-Irving, Mabile, et al., 2013; Taylor-Robinson et al., 2018). Our findings indicate a significant association between adverse childhood experiences and increased mortality risk (OR, 1.64; 95 %CI, 1.51 to 1.78; P < 0.001). Existing research primarily investigates the mechanisms from two perspectives: biology and behavior. Biologically, adverse childhood experiences might act as chronic stressors, continuously activating the allostatic systems, including neural, endocrine, and immune systems, thereby resulting in allostatic load or overload (McEWEN, 1998; Danese and McEwen, 2012). Consequences include structural and functional abnormalities in the prefrontal cortex and hippocampus, activation of the hypothalamic-pituitary-adrenal axis, or an augmentation of inflammatory markers. Increasing evidence emphasizes the modifications in brain structure and function, with ongoing research exploring their links with psychopathology (Pechtel and Pizzagalli, 2011; McCrory et al., 2017; Yu et al., 2021). Different types of adverse childhood experiences target distinct neural pathways selectively. (Teicher and Samson, 2016). Behaviorally, children exposed to adverse childhood experiences are more likely to develop internalizing (e.g., anxiety, depression) and externalizing (e.g., substance abuse, social difficulties, aggression, promiscuity) behaviors due to impairments in social, emotional, and cognitive systems (Jewkes et al., 2010; Houtepen et al., 2020; Hays-Grudo et al., 2021). This is consistent with our findings, which indicate higher risks for external cause mortality (OR, 1.91; 95 % CI, 1.7 to 2.15; P < 0.001) compared to internal cause mortality (OR, 1.3; 95 % CI, 1.17 to 1.44; *P* < 0.001). Further analysis indicated a significant association between adverse childhood experiences and an increased risk of suicide mortality, consistent with previous findings (Sahle et al., 2022). Wang et al. (2023) found that female nurses with a history of severe physical abuse or sexual abuse faced elevated risks of injury, poisoning, and suicide mortality. A prospective cohort study involving 2223,927 individuals identified accidents and suicide as the leading causes of death among those with multiple adversities (Rod et al., 2020). This highlights the need for effective management of risky behaviors and the integration of suicide prevention strategies in interventions.

Among trauma patients, those exposed to adverse childhood experiences had a twofold higher risk (OR, 3.52; 95 % CI, 2.05 to 6.03; P <0.001) of mortality compared to those not. This vulnerable group warrants more tailored interventions in clinical settings. A subgroup analysis revealed a significant association between adverse childhood experiences before age 13 and increased mortality. However, comparing the effects between childhood and adolescence was not feasible due to the limited number of studies focusing on adolescence. A cohort study of 605,344 individuals found that adverse experiences in early adolescence were more strongly associated with later adverse outcomes than those in early childhood (Andersen, 2021). Future research could improve understanding by further analyzing the distinct impacts at different developmental stages. Furthermore, studies using retrospective self-reports to assess adverse childhood experiences reported a significantly lower pooled effect size than those using objective records. This discrepancy is likely due to recall and reporting biases influenced by participants' personality traits and dispositions (Hardt and Rutter, 2004; Reuben et al., 2016). Our meta-regression results showed that regional variations do not significantly contribute to heterogeneity. Despite this, previous research has demonstrated that race and culture correlate with the prevalence of adverse childhood experiences (Merrick et al., 2018). Cultural variations in parenting could influence family interactions (Bornstein, 2012). Unfortunately, the studies included do not provide sufficient information to analyze the potential role of culture in mitigating the risks associated with adverse childhood experiences and mortality. Future research should consider cultural aspects as potential protective factors (Radford et al., 2022).

The results showed those exposed to maltreatment had a higher risk for mortality (OR, 1.95; 95 % CI, 1.65 to 2.3; P < 0.001). Significant correlations were observed in both men and women, across both internal and external causes of mortality. Both physical and sexual abuse were associated with increased mortality. Our findings contradict a previous systematic review, which reported no statistically significant association between physical, emotional, and sexual abuse and mortality risks (D'arcy-Bewick et al., 2022). The review also found notable gender disparities. In our study, following a thorough sensitivity analysis, the association between maltreatment and mortality among men exhibited instability. A previous longitudinal study of 6285 individuals over 20 years revealed no significant associations between moderate and severe physical or emotional abuse and mortality in men (Chen et al., 2016). Another study reported that early adverse experiences had a more pronounced impact on women's later-life health compared to men (Lee and Ryff, 2019). Physiological mechanisms, including genetic and hormonal differences, suggest that women may be more sensitive to stress and at higher risk of developing affective disorders (Bale and Epperson, 2015). Furthermore, early adversity appears to influence women's lifestyle and health-related resources more strongly (Lee and Ryff, 2019). Further research is needed to elucidate the underlying mechanisms and guide the allocation of health resources. Three studies reported that smoking played a partial mediating role in the relationship between physical abuse and mortality (Rogers et al., 2021; Bhattarai et al., 2023; Wang et al., 2023). Providing enhanced support for smoking cessation is essential for this group. Furthermore, future research should investigate additional factors, such as depression and post-traumatic stress disorder, that link adverse childhood experiences to mortality. Identifying these mediators could guide the development of targeted interventions like mindfulness therapy (Ortiz and Sibinga, 2017).

The pooled effect size for household dysfunction and mortality (OR, 1.36; 95 % CI, 1.22 to 1.51; *P* < 0.001) was marginally smaller compared to that of maltreatment and mortality (OR, 1.95; 95 % CI, 1.65 to 2.3; P < 0.001). A cross-sectional study highlighted that the consequences of household dysfunction were mediated partly or completely by maltreatment (Clemens et al., 2019). Another study observed that once controlling for maltreatment, the influence of household dysfunction on mental health became non-significant (Negriff, 2020). Further research is required to clarify the exact relationship between these factors. The findings also highlighted a significant association between household dysfunction and external cause mortality, particularly suicide. Findings from a large-scale cohort study indicated that parental psychiatric disorder, parental criminality, and suicide in the family were associated with the highest risk of adolescence suicide (Björkenstam et al., 2017). In addition, household dysfunction is identified as a risk factor for involvement with child welfare services. We found that children who received out-of-home care had a higher risk of mortality (OR, 2.87; 95 % CI, 2.12 to 3.9; P < 0.001) compared to those not. The efficacy of out-of-home care, originally designed as a secure sanctuary for children, has raised concerns (Brännström et al., 2020). Segal et al. (2021) found that children placed in out-of-home care after the age of three exhibited a higher risk of mortality compared to those placed in care before the age of three. Improving the current welfare services to safeguard children from adverse effects across the life course is a crucial priority.

A significant link between low socioeconomic status during childhood and mortality was observed, supporting a previous systematic review (Galobardes et al., 2004). While some studies (Jackisch et al., 2019; Lee and Ryff, 2019; D'Arcy-Bewick et al., 2023) did not establish an association between low socioeconomic status in childhood and mortality, the bulk of research highlights the powerful influence of socioeconomic status on health outcomes (Wickham et al., 2016; Schmidt et al., 2021). Our study revealed a significant association between low socioeconomic status and mortality in men, while no significant association was observed in women. This finding contradicts previous research, which suggested that low socioeconomic status had a greater impact on mortality among women (Pudrovska and Anikputa, 2014). However, some studies found that childhood socioeconomic status had a greater impact on men's immune and cognitive function (Lyu, 2015; Gassen et al., 2021). The gender differences remain to be explored.

Given the close relationship between adverse childhood experiences and mortality, early implementation of evidence-based interventions is imperative. Nevertheless, numerous challenges remain that necessitate attention and resolution. A systematic review (Loveday et al., 2022) has demonstrated that there is inadequate evidence to support the benefits of screening for adverse childhood experiences, and significant controversy exists regarding whether screening should be conducted (Campbell, 2020a, 2020b; Harris, 2020). In addition, due to the lack of targeted interventions for different subtypes, insufficient effectiveness, and limited healthcare resources, the current state of interventions remains suboptimal (Korotana et al., 2016; McDermott et al., 2023). In the development of future public policy, it is crucial to enhance resource allocation and strengthen multi-sectoral collaboration to prevent and alleviate the impacts of adverse childhood experiences. This is also regarded as cost-effective (Peterson et al., 2023).

This study has several strengths, including a large total sample size and the pooling of effect sizes extracted from fully adjusted models. However, it also has limitations that warrant attention. Firstly, the results should be interpreted with caution due to substantial heterogeneity. Despite extensive subgroup analyses, substantial heterogeneity was observed in most of the results. The complexity of this heterogeneity is exacerbated by the diverse and varied adjustment factors employed across the studies. Nevertheless, the meta-regression analysis has revealed several factors driving heterogeneity. Secondly, publication bias might impact the reliability of certain results in the study. Although, the trim-and-fill analysis indicated that no additional studies needed to be included. Furthermore, some studies used retrospective self-reports, which might be subject to recall or reporting bias. Finally, like other studies (Bellis et al., 2019; Hughes et al., 2017, 2021), our search terms could not encompass all subtypes of adverse childhood experiences, which could potentially result in missing relevant research.

5. Conclusions

In conclusion, adverse childhood experiences are associated with overall mortality, external cause mortality, and internal cause mortality. The subtypes, including maltreatment, household dysfunction, low socioeconomic status, and out-of-home care are also linked with increased mortality. Statistically significant gender differences were not revealed in the results, except for minor variations observed within the low socioeconomic status. In addition, adverse childhood experiences appear to have a greater impact on external cause mortality. However, the association between specific combinations of adverse childhood experiences and mortality remains unclear and requires further investigation. Further research is warranted to confirm the mechanisms and trajectories underlying the relationship between adverse childhood experiences and mortality.

CRediT authorship contribution statement

Lishuang Zheng: Writing – review & editing, Writing – original draft, Investigation, Data curation. Peiqi Liu: Investigation, Formal analysis. Xin Li: Investigation, Formal analysis. Shoumeng Yan: Formal analysis, Data curation. Yiming Qiu: Validation. Yiran Xu: Data curation. Yali Yang: Visualization. Li Chen: Methodology, Formal analysis, Data curation, Conceptualization. Guichen Li: Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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