allergies

Systematic Review

The Relationship between Adverse Childhood Experiences and Non-Asthmatic Allergies: A Systematic Review

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Abstract: Since the publication of the Adverse Childhood Experiences (ACEs) Study in 1998, there has been a dramatic increase in the number of studies exploring the immunoendocrinological sequelae of toxic stress. However, the literature exploring this in relation to paediatric atopy predominantly revolves around asthma. This review aims to (1) explore the association between ACEs and non-asthmatic, non-iatrogenic paediatric allergies (NANIPA) in the developed world and (2) further focus on the association between exposure to violence and NANIPA. Methods: PubMed and Scopus were searched for articles examining adversity and NANIPA before age 18. Non-English papers, publications before 1998, reviews, opinion pieces and case reports/series were excluded. Screening, data extraction, and risk-of-bias were independently reviewed by the first two authors. Results: Nine of the one thousand eighty-nine records identified were included. Four pertained to objective 1, four to objective 2, and one pertained to both. Regarding objective 1, all studies reported a positive dose-response relationship between ACEs and NANIPA, which was most significant among preschoolers and diminished with age. Studies relevant to objective 2 were too heterogenous to compare. However, two interesting associations emerged: (1) The types of violence significantly associated with NANIPA in adolescence differ in a sex-dependent manner, and (2) verbal abuse and bullying are the violence types most powerfully and significantly associated with NANIPA. Conclusion: Psychological stress is a probable IgE-independent driver of atopy in children exposed to adversity and/or violence. While the literature is too underdeveloped to allow for meaningful cross-comparison between studies, this review has identified many interesting areas for future research.

Keywords: adverse childhood experience; childhood adversity; toxic stress; paediatric allergy; paediatric atopy

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1. Introduction

In 1998, CDC and Kaiser conducted a massive cohort study to investigate the relationship between exposure to adverse childhood experiences (ACEs) such as abuse, neglect, and household dysfunction, and adult health outcomes [1]. Of its many findings, two big takeaways emerged: Firstly, ACEs were far more prevalent than expected—with 52.1% of participants reporting > 1 exposure. Secondly, a significant dose-response relationship between total ACE exposure and a myriad of health outcomes—ranging from suicide to cancer—was found [1].

The subsequent upsurge of research interest in ACEs continues to the present day, with recent literature suggesting that ACE exposure is a major contributor to the global

burden of disease and disability, with the increasing number of ACEs one is exposed to, the higher the risk to the individual's health and morbidity later in life [2,3]. This is alarming as a 2023 meta-analysis of 206 studies estimated that 22% of people have experienced one ACE, 13% two ACEs, 9% three ACEs, and 16% four or more. We must strive to better understand how "prolonged, or repetitive adversity with a lack of necessary nurturance [. . .] to prevent an abnormal stress response" disrupts the complex neuroendocrine immune circuitry of the developing child by inducing a prolonged hypercortisolic and proinflammatory state. This phenomenon, termed toxic stress, results in aberrations ranging from a neuroanatomical level to an epigenetic one—thereby setting the stage for downstream adult health consequences [4].

Similar to studies investigating adult health outcomes, there is a growing research interest in the relationship between toxic stress and paediatric health. Not all childhood illnesses have been similarly explored—of relevance to this review are non-asthmatic, non-iatrogenic paediatric allergies (NANIPA).

This review aims to explore the relationship between the following:

Objective 1: Cumulative ACE exposure and NANIPA in the developed world. As per the 1998 study and the wider literature, ACE refers to the total number of ACE types experienced;

Objective 2: Childhood violence and NANIPA in the developed world.

2. Methods

This review follows the PRISMA 2020 reporting guidelines [5], as outlined below.

2.1. Eligibility Criteria

In order to be considered, cases had to adhere to each of the following criteria:

2.1.1. Population of Interest

(i) Paediatric (aged < 18); and (ii) developed countries (>0.8 on the United Nations Human Development Index of 2022 [6]).

2.1.2. Exposure to Either or Both of the Following

(i) Objective 1 (ACE): Any adversity criteria in keeping with or which expands upon the original 10 ACEs from the 1998 CDC–Kaiser study (10 ACEs). Studies deviating from the aforementioned were included a posteriori on a case-by-case basis;

(ii) Objective 2 (Childhood violence): Violence, as defined by the World Health Organization [7], experienced/witnessed by the child (Violence Prevention Alliance Approach).

2.1.3. NANIPA (>1 of the Following)

(i) Physician-made diagnosis; (ii) documented health records; (iii) positive caretaker report; (iv) positive self-report by children above age seven [8].

Cases were excluded if they met one or more of the following criteria: (i) Publications before 1998; (ii) non-English language; (iii) case reports/series, opinion pieces, review articles; (iv) studies limiting adversity exposure to the antenatal period; or (v) a posteriori additions (studies which fail to stratify NANIPA as a specific dependent variable, and/or studies exploring adversity as a dependent variable). These limitations were selected to set out the scope of the study in accordance with the researchers' limited resources, access to data, and data quality.

2.2. Data Sources and Search Strategy

PubMed and Scopus were searched, and two unique query strings were tailored (see Tables 1 and 2). Both were independently reviewed by all authors. To maximise sensitivity, this review included asthma in its query string. Papers focused solely on asthma were subsequently excluded.

Table 1. Final query string for PubMed.

	MeSH		*Key Words*
Population	"Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]	**OI**	"Infan*"[tiab] OR "Baby"[tiab] OR "Neonat*"[tiab] OR "Child*"[tiab] OR "Toddler*"[tiab] OR "Preschooler*"[tiab] OR "Teen*"[tiab] OR "Adolescent*"[tiab]
Exposure	"Intimate Partner Violence"[Mesh] OR "Domestic Violence"[Mesh] OR "Adverse Childhood Experiences"[Mesh] OR "Shaken Baby Syndrome"[Mesh] OR "Battered Child Syndrome"[Mesh] OR "Child Protective Services"[Mesh] OR "Bullying"[Mesh]	**OR**	"Intimate partner violence"[tiab] OR "Household abuse"[tiab] OR "Household violence" [tiab] OR "Domestic abuse"[tiab] OR "Domestic violence"[tiab] OR "Sexual abuse"[tiab] OR "Sexual violence"[tiab] OR "Physical abuse"[tiab] OR "Physical violence"[tiab] OR "Child abuse" OR "Child maltreatment"[tiab] OR "Child prot*"[tiab] OR "Non-accidental injury"[tiab] OR "Adverse childhood*"[tiab] OR "Community violence"[tiab] OR "Bullying"[tiab]
Outcome	"Hypersensitivity, Immediate"[Mesh] OR "Hypersensitivity, Delayed"[Mesh]	**OI**	"Hypersensitivity"[tiab] OR "Allergy"[tiab] OR "Atopy"[tiab] OR "Allergic"[tiab] OR "Atopic"[tiab] OR "Eczema"[tiab] OR "Rhinitis"[tiab] OR "Asthma"[tiab] OR "Anaphylaxis"[tiab] OR "Urticaria"[tiab]
Final query string: *"Population" AND "Exposure" AND "Outcome"*			

*: Adjusted for non-response.

Table 2. Final query string for Scopus.

Population	***("Infant*" OR "Baby" OR "Neonat*" OR "Child*" OR "Toddler*" OR "Preschool*" OR "Teen*" OR "Adolescent*")***
Exposure	("Adverse childhood*" OR "ACE*") OR ("Intimate partner" OR "Household" OR "Domestic" OR "Child" OR "Physical" OR "Sexual" OR "Community") PRE/5 ("Abuse" OR "Violence" OR "Maltreatment") OR ("Non-accidental injury" OR "NAI" OR "Child prot*" OR "Bullying")
Outcome	("Hypersensitivity" OR "Allergy" OR "Atopy" OR "Allergic" OR "Atopic" OR "Eczema" OR "Rhinitis" OR "Asthma" OR "Anaphylaxis" OR "Urticaria")
Final query string: *"Population" AND "Exposure" AND "Outcome"*	

*: Adjusted for non-response.

2.3. Study and Data Extraction

The first and second authors independently screened unique records by title and abstract. Records that adhered to the eligibility criteria then underwent full-text retrieval.

The following were extracted:

Study details: First author; publication date; study objective, design, and setting;

- Source population: Key characteristics; representativeness;
- Study sample: Sample size; eligibility criteria;
- Exposure: Specific exposure types; assessment tool used; criteria for positive exposure;
- Outcome: Specific NANIPA type(s); assessment tool used; criteria for positive outcome;
- Results: Descriptive statistics; covariates; aOR; 95% CI; *p*-value; key findings/limitations.

Extracted data were thrice reviewed by the first author, and independently reviewed once by the second author. Statistical queries were directed to an on-site medical statistician.

2.4. Data Synthesis

Studies were narratively stratified according to the review's two objectives. Of note is the study by McKenzie and Silverberg [9] which is relevant to both objectives and was likewise stratified. Descriptive statistics, covariates, and an exposition of each study's exposure criteria are separately tabulated (Tables 3 and 4). To contend with the heterogeneity of the studies included in objective 2, extracted data underwent two further levels of stratification: First by exposure criteria, secondly by the outcome reported.

Table 3. Detailed exposure criteria, descriptive statistics, and covariates for studies included for objective 1.

	McKenzie et al., 2020, US [9]	Thakur et al., 2020, US [10]	Turney [1], 2020, US [11]	Bellis et al., 2018, Wales [12]	Feng et al., 2019, Taiwan [13]
Adversity definition	**As per the 10 ACEs:** Verbal abuse, Physical abuse, Sexual abuse, Physical/emotional neglect, Caregiver depression, Parental separation/divorce, Caregiver incarceration, Caregiver substance abuse	**Seventeen-item PEARLS screener** **10 ACEs** **Seven related life events (RLE):** Neighborhood violence, Housing instability, Food insecurity, Discrimination, Caregiver physical illness, Forced separation, Caregiver death	**Modified from 10 ACEs:** Income difficulties, Parental divorce/separation, Parental death, Parental incarceration, Domestic violence, Neighborhood violence, Household member mental illness; Household member substance abuse; Racial discrimination	**Adversity:** 10 ACEs **Resilience assets:** Community help, Given opportunities, Fair treatment, Culturally engaged, Supportive friends, Role model, Trusted adult available	**Seven externally validated victimisation types (derived de novo from prior pilot study):** Neglect, Psychological violence, Physical abuse *, Sexual violence, Intimate partner violence, Bullying, Community violence **High threshold for physical abuse:** e.g., Hit with hard object ≥ 3x in 1y
Descriptive statistics	**CAE prevalence categorised as follows:** **0 ACEs ǀ 1 ACE ǀ 2 ACEs ǀ ≥ 3 ACEs** **@ 5y follow-up:** 36.3% ǀ 30.9% ǀ 19.7% ǀ 13% **@ 9y follow-up:** 29.2% ǀ 30.5% ǀ 22.8% ǀ 17.5% **@ 15y follow-up:** 19.9% ǀ 39.3% ǀ 25.1% ǀ 15.8%	76% of participants reported a Total PEARLS score ≥ 1 **Median PEARLS score (IQR):** 2 (1–5)	**CAE prevalence categorised as follows:** • **0 ACEs:** 54.7% • **1 ACE:** 24.7% • **2 ACEs:** 10.1% • **≥3 ACEs:** 10.5% **Lifetime prevalence of NANIPA increased with CAE** * **Note:** Weighted samples used i. **0 ACEs:** 16.3% ii. **1 ACE:** 19.3% iii. **2 ACEs:** 25.1% iv. **≥3 ACEs:** 26.9%	**CAE prevalence categorised as follows:** • **0 ACEs:** 51.5% • **1 ACE:** 18.9% • **2–3 ACEs:** 16.2% • **≥4 ACEs:** 3.4% **Resilience prevalence:** • **All 7 assets:** 48.3% • **<2 assets:** 9.7% **Overall NANIPA prevalence:** 19% **NANIPA prevalence increased with CAE (X^2: 14.9, $p < 0.005$)** • **0 ACEs:** 15.4% • **1 ACE:** 17.9% • **2–3 ACEs:** 20.6% • **≥4 ACEs:** 32.3%	**1y-prevalence of poly-victimisation:** **0 victimisations:** 9.7% **1 victimisation:** 19.3% **2 victimisations:** 21.7% **≥3 victimisations:** 48%
Covariates adjusted for	Child's sex, race, asthma history status; Household income	Child's age, sex, race; Caretaker's education; Household income	Child's age, sex, race, birth weight, immigration status, health insurance, regular place of medical care. Parental age, education, employment, health. Marital status, smoking; Neighborhood safety	Age, sex, ethnicity, Deprivation quintile	Child's sex, neonatal complications, Parental marital status, Household mental illness, Household addiction, Household incarceration

[1]: 95% CI unreported. *: Adjusted for non-response.

Table 4. Detailed exposure criteria, descriptive statistics, and covariates for studies included for objective 2.

	McKenzie et al., 2020, US [9]	*Haavet et al., 2004, Oslo* [14]	*McLaughlin et al., 2016, US* [15]	*Gartland et al., 2021, Melbourne* [16]	*Jennings et al., 2017, South Korea* [17]
Violence definition	As detailed in "Results"	As detailed in "Results"	**Direct violence (as inflicted unto the child):** Physical/Sexual violence, IPV, getting robbed, getting stalked **Indirect violence (as witnessed by the child):** Domestic violence, Community violence **Any violence:** Direct/Indirect violence	**Composite abuse scale for IPV (1-year prevalence):** • ≥1 maternal report of physical abuse, OR • ≥3 maternal reports of emotional abuse **Timing of IPV exposure:** • **Never** • **Early:** @ 1y and/or 4y F/U • **Recent:** @ 10y F/U	**Verbal BV:** Never vs. "Severely teased and/or verbally threatened" **Physical BV:** Never vs. "Beaten by others" **Verbal BP:** Never vs. "Severely teased and/or verbally threatened others" **Physical BP:** Never vs. "Beats others"
Descriptive statistics	**Descriptive statistics** • 1-year prevalence rate of AD remained fairly constant across the 5y, 9y, and 15y F/U (14.8%, 15.1%, 14.2% respectively) • No significant sex differences noted	**Violence prevalence (Boys ǀ Girls ǀ Total)** Bullying (15% ǀ 14% ǀ 15%) Physical violence (29% ǀ 16% ǀ 22%) * Sexual violence (2% ǀ 6% ǀ 4%) * *** Difference between the 2 genders was statistically significant (*p*-value unreported)** **NANIPA prevalence (For boys ǀ For girls ǀ Overall)** • Hay fever (36% ǀ 40% ǀ 38%) * • Eczema (23% ǀ 34% ǀ 29%) * *** Difference between the 2 genders was statistically significant (*p*-value unreported)**	**Lifetime violence prevalence by gender (Boys ǀ Girls ǀ Overall) *** * Gender differences were non-significant **Any violence:** 24.3% ǀ 25.7% ǀ 25% **Direct violence:** 13.5% ǀ 13.3% ǀ13.4% **Indirect violence:** 11% ǀ 7.84% ǀ 9.4%	**IPV categories/prevalence:** • **No IPV reported:** 71.3% • **Early exposure:** 12.7% • **Recent exposure:** 16% **Prevalence for allergy: % (95% CI)** • **None:** 84.4 (81.3–87.4) • **Allergy:** 15.6 (12.6–18.7)	**Descriptive statistics for exposure variable @ wave 3 (M, SD):** • **Verbal BV:** 0.041, 0.198 • **Physical BV:** 0.013, 0.115 • **Verbal BP:** 0.04, 0.197 • **Physical BP:** 0.006, 0.079 **Descriptive statistics for outcome variable @ waves 1 and 4 (M, SD)** • **Wave 1:** 0.318, 0.502 • **Wave 4:** 0.344, 0.516
Covariates adjusted for	As detailed in Table 3	Unspecified	Sex, Age, Race, Parental education, Household income, Lifetime mental disorders	Child sex, Maternal education	Gender, Household income, Parental care, Peer relations, Teacher relations, Baseline illness

2.5. Risk of Bias Assessment

The first two authors each independently performed a risk of bias assessment. As per the recommendations of a 2019 review comparing the risk of bias assessment tools [18], this review uses the validated Joanna Briggs Institute [19] checklists for cross-sectional and cohort studies.

Assessment of certainty was carried out by the third and fourth authors. The level of evidence for this study was established using the application GRADE (Grading of Recommendation Assessment, Development and Evaluation). This system categorises evidence into four levels: high, moderate, low, and very low (Table 5). The level of evidence is impacted negatively by five criteria: reporting bias, imprecision, study limitations, inconsistency of results, and indirectness of evidence. Conversely, there are three criteria that can elevate the calibre of evidence: a substantial effect size, a discernible dose-response trend, and plausible residual confounding.

Table 5. Quality Levels Defined.

Quality Level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

3. Results

3.1. Study Selection

Automated screening and duplicate removal yielded 706 unique records for title/abstract screening (see Figure 1).

Six hundred eighty-five failed to meet the eligibility criteria, and twenty-one underwent full-text retrieval—one of which could not be retrieved in English. A full-text review of the remaining 20 reports resulted in 11 additional exclusions.

3.2. Results

Of the nine included studies, eight were published in the last decade and one in 2004. Four studies were conducted in the US, and five were conducted in Wales, Norway, Australia, Taiwan, and South Korea. Six were cross-sectional studies, and three were longitudinal studies. The selected studies were as follows:

1. McKenzie and Silverberg, 2020 [9];
2. Thakur et al., 2020 [10];
3. Turney, 2020 [11];
4. Bellis et al., 2018 [12];
5. Feng, 2019 [13];
6. Haavet, Straand, Saugstad, and Grünfeld, 2007 [14];
7. McLaughlin et al., 2016 [15];
8. Gartland et al., 2021 [16];
9. Jennings, Song, Kim, Fenimore, and Piquero, 2017 [17].

Of the five included studies, two ([9,10]) investigated ACE's association with allergic rhinitis (AR) and/or allergic dermatitis (AD) specifically, and three [11–13] explored its association with NANIPA. Regardless of the outcome studied, all studies clearly demonstrated a positive association—the significance and strength of which increased with ACE in a dose-dependent manner. Two ([9,10]) of the five studies further stratified the analysis

by age and found that the significance and strength of the association was stronger in lower age groups, peaking among preschoolers (Table 6).

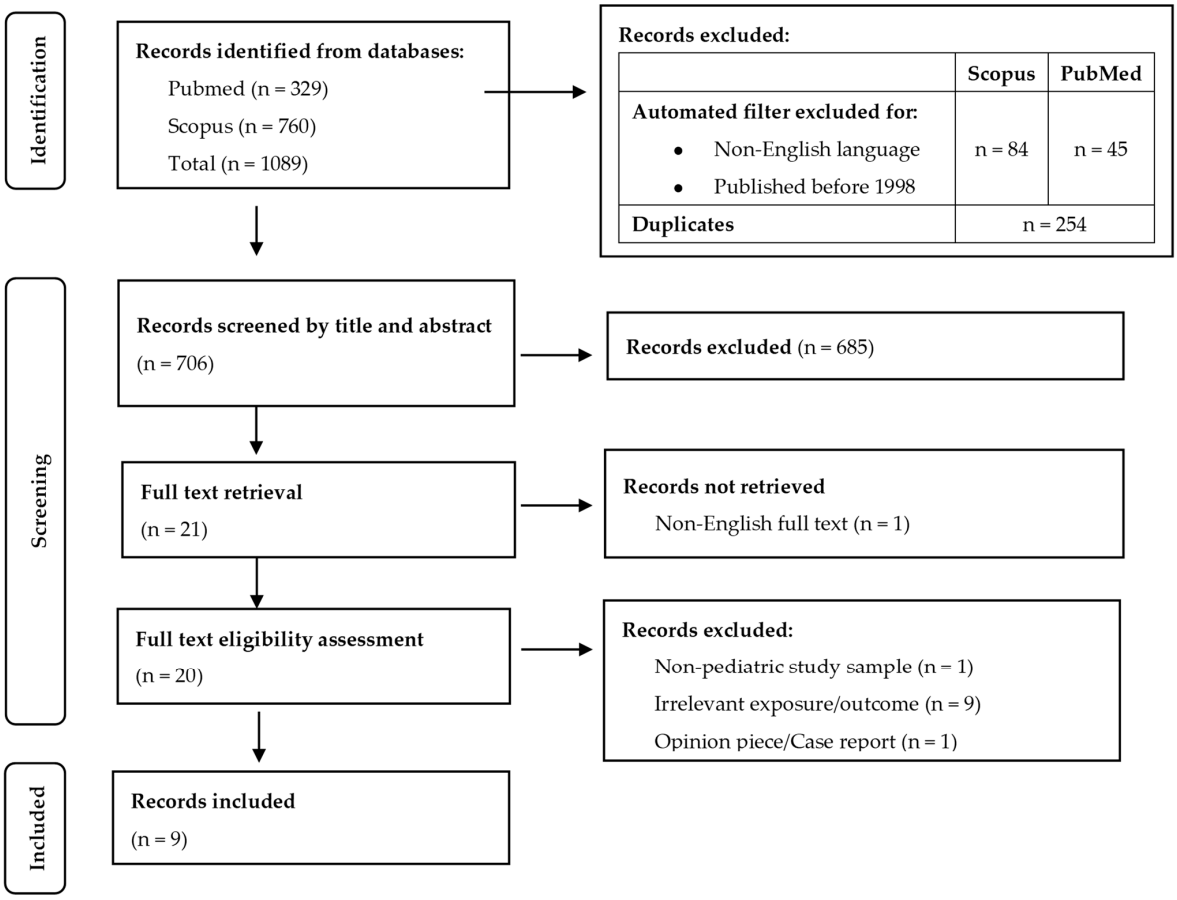

Figure 1. PRISMA 2020 Study Selection Flowchart.

One study ([12]) also examined stress-mitigating factors (termed "resilience assets") and found that these factors may weaken the association between ACE and NANIPA.

The five studies included are notably heterogenous predominantly due to their inconsistent use of exposure/outcome criteria and assessment tools as follows(Table 7):

Two ([9,14]) classified violence by type (e.g., Sexual, physical, verbal, etc.);

One ([15]) classified violence experientially (child-witnessed and/or child-directed);

One ([16]) investigated witnessed violence specifically as intimate partner violence (IPV);

One ([17]) classified violence both experientially and by type but limited its focus to bullying (Verbal vs. physical violence, child-directed vs. child-perpetrated).

Only studies investigating child-directed violence reported significant results ([9,14,15,17]). McKenzie and Silverberg ([9]) and Jennings, Song, Kim, Fenimore, and Piquero (9 [17]) included verbal violence in the analysis. Both reported that verbal violence is the strongest and most significant violence type associated with AD and AR, respectively. McKenzie and Silverberg ([9]) also showed that this association peaked in preschoolers and diminished with age.

Haavet et al. ([14]) and McLaughlin et al. [15] investigated for sex-specific differences. The former found that (i) the 1-year prevalence of physical violence was twice as high in 15-year-old boys than girls, (ii) the 1-year prevalence of sexual violence was three times as high in 15-year-old girls than boys, and (iii) AD and AR were significantly and positively associated with physical violence only in boys, and with sexual violence only in girls.

Conversely, the latter reported no significant sex-specific associations. Notable, however, is the restriction of its analysis to the experiential classification of violence.

Table 6. Objective 1—CAE and NANIPA.

	McKenzie et al., 2020, US [9]	**Thakur et al., 2020, US [10]**	**Turney [1], 2020, US [11]**	**Bellis et al., 2018, Wales [12]**	**Feng et al., 2019, Taiwan [13]**
Aim:*To assess the association between*	1. CAE and eczema 2. Each adversity type and eczema	CAE and child health	CAE and child health	CAE/Resilience assets and child health	Poly-victimization and health outcomes in 4th graders
Design	Secondary analysis of a prospective birth cohort study	XS study secondary to parent RCT	Secondary XS analysis of a national-level survey	XS survey	XS survey
Population	Mother/child dyads born in 20 large US cities (1998–2000)	Caretaker/child (3m–11y.o) dyads presenting for well-child checks in a single-centre pediatric safety net setting in Oakland, California	Representative of US non-institutionalized caretaker/child dyads from 2016 to 2017	All Welsh households	All 4th graders (10–11y.o) in coterminous Taiwan (2013–2014 academic year)
Sample Size ***Inclusion criteria*** ***Exclusion criteria***	N = 4898 F/Us in which 1y-history of AD was reported Participants with missing data	N = 367 * All participants who underwent adversity screening in parent RCT Participants with missing outcome data	N = 71,811 †,‡ N.A. N.A.	N = 2452 18–69y.o cognitively able to complete survey Participants with missing data	N = 6233 Signed consent from parent/child A posteriori exclusion of children with BMI-for-age Z-score < 4 or >5
Exposure (CAE) ***Exposure*** ***Positive exposure*** ***Data type***	10 ACEs (1y prevalence) **Physical/verbal abuse and neglect:** • **5 and 9y F/U:** Parent/child Conflict Tactics Scale • **15y F/U**: Child completed survey § **Sexual abuse**: New child protective service involvement ‖ **Household dysfunction:** Caretaker-report Categorical	**Seventeen-item PEARLS screen (lifetime prevalence) stratified as:** • 10 ACEs (ACE) • Seven related life events (RLE) • Total PEARLS (PEARLS) **Positive caretaker report** Categorical/continuous	Modified from the 10 ACEs as per survey methodologist advice (Lifetime prevalence) **Positive caretaker report** Categorical	Lifetime prevalence of: • 10 ACEs • Resilience assets **Self-reported exposure occurring before age 18:** • **Adversity:** CDC ACE tool • **Resilience:** Survey adapted from "Child Youth and Resilience measure" ‖ Categorical	Seven victimisation types (1y-prevalence) **Child-completed, externally validated de novo survey** Continuous

Table 6. *Cont.*

	McKenzie et al., 2020, US [9]	**Thakur et al., 2020, US [10]**	**Turney [1], 2020, US [11]**	**Bellis et al., 2018, Wales [12]**	**Feng et al., 2019, Taiwan [13]**
Results Outcomes Diagnosis criteria aOR (95% CI)	AD Positive caretaker report (1y-prevalence) **CAE and AD association @ 5y F/U:** • **1 ACE:** 1.42 (1.08–1.86) • **2 ACEs:** 1.49 (1.10–2.02) • **≥3 ACEs:** 2.10 (1.52–2.89) **CAE and AD association @ 9y and 15y F/U**: Association diminished with age and was **only significant for 9y.o with ≥3 ACEs**: 1.48 (1.09–2.01)	AR, AD The International Study of Asthma and Allergies in Childhood questionnaire (Lifetime prevalence) **CAE and AR association (ACEs):** • **ACEs as continuous variable:** 1.12 (1.00–1.25) • **1–3 ACEs:** 2.36 (1.35–4.13) • **≥4 ACEs:** 2.40 (1.22–4.74) **CAE and AR association non-significant in "RLE" and "PEARLS" strata.** **CAE and AD association (ACEs):** • **ACEs as continuous variable:** 1.16 (1.04–1.29) • **1–3 ACEs:** 2.19 (1.32–3.65) • **≥4 ACEs:** 2.75 (1.44–5.23) **CAE and AD association (RLE):** 1.24 (1.04–1.47) **CAE and AD association (PEARLS):** 1.11 (1.03–1.20)	NANIPA Caretaker–report of physician diagnosis (Lifetime prevalence) **CAE and NANIPA association (0–17y):** **1 ACE:** aOR 1.17, $p < 0.05$ **2 ACE:** aOR 1.46, $p < 0.01$ **≥3 ACE:** aOR 1.49, $p < 0.01$ **CAE and NANIPA association (6y.o):1 ACE:** aOR 1.17, $p > 0.05$ **2 ACE:** aOR 3.25, $p < 0.001$ **≥3 ACE:** aOR 2.35, $p < 0.01$ **CAE and NANIPA association (12, 17y.o):** • Non-significant across all CAE categories • Strength significantly reduced with age	NANIPA Self-reported NANIPA occurring before age 18 **CAE and NANIPA adjusted for demographics only:** • **1 ACE:** 1.17 (0.88–1.55), $p = 0.29$ • **2–3 ACEs:** 1.35 (1.01–1.81), $p < 0.05$ • **≥4 ACEs:** 2.47 (1.87–3.28), $p < 0.001$ **CAE and NANIPA adjusted for demographics and significant resilience assets [2]** • **1 ACE:** 1.14 (0.86–1.52), $p = 3.6$ • **2–3 ACEs:** 1.26 (0.94–1.69), $p = 0.13$ • **≥4 ACEs:** 2.05 (1.51–2.77), $p < 0.001$	NANIPA Child-reported NANIPA [¶] **Poly–victimisation and NANIPA:** • **aOR:** 1.04 • **95% CI:** 1.01–1.07 • $p = 0.007$

Table 6. *Cont.*

	McKenzie et al., 2020, US [9]	Thakur et al., 2020, US [10]	Turney [1], 2020, US [11]	Bellis et al., 2018, Wales [12]	Feng et al., 2019, Taiwan [13]
Key findings	**1.** 1y-prevalence of CAE and AD have a significant dose-response association. **2.** This relationship persisted across all three F/Us but was strongest and most significant at 5y.	**1.** CAE and AR have a significant dose-response association for the "ACEs only" measure. **2.** CAE and AD have a significant dose-response association across all three measures.	**1.** CAE and NANIPA have a significant dose-response association for 0–17y.o **2.** This relationship persisted across all three age-specific strata but was significant only for 6y.o and diminished with age **3.** AOR and NANIPA significantly different odds ratios across the three specific ages analysed.	**1.** CAE-and-NANIPA have a significant dose-response association, except for those with only one ACE exposure. **2.** This relationship was lowered after adjusting for significant resilience assets.	**1.** Staggeringly high prevalence of poly-victimisation was reported despite the study using (i) a higher threshold for physical abuse and (ii) a 1y-prevalence window (Table 3) **2.** Results may be confounded by lifestyle factors (e.g., smoking).
Limitations	**1.** Cross-comparability limited by 1y-prevalence. **2.** Natural progression of NANIPA may cause confounding at older ages.	**1.** Inadequate statistical power to determine potential age/gender differences. **2.** Possibility of response bias due to low response rate in parent study (41%). **3.** Generalizability of results limited by single centre design and pediatric safety net setting.	**1.** Modified ACE criteria used limits cross-comparability. **2.** Association of specific ACEs and NANIPA not assessed. **3.** Natural progression of NANIPA may cause confounding at older ages.	The use of adults to retrospectively recall exposures/outcomes: • Limits cross-comparability • Increases recall bias and childhood amnesia	**1.** Limited cross-comparability with Western studies. **2.** Outcome prevalence window was unspecified. If it predates the 1y-prevalence window used for exposure, results may be unsound.

Results in sub-script are non-significant. *: Adjusted for non-response; †: Adjusted for non-response and missing data; ‡: Weighted sample used; §: Validity unspecified; ||: Unvalidated; ¶: Prevalence window unreported. [1]: 95% CI unreported. [2]: Only "Fair treatment" was associated with significantly lower NANIPA odds: 0.61 (0.46–0.81); $p < 0.001$.

Table 7. Objective 2—Violence and NANIPA.

	McKenzie et al., 2020, US [9]	Haavet et al., 2004, Oslo [14]	McLaughlin et al., 2016, US [15]	Gartland et al., 2021, Melbourne [16]	Jennings et al., 2017, South Korea [17]
Aim: *To assess the association between:*		Negative life experiences and common illnesses among 15y.o in Oslo, Norway	1. How violence is experienced and chronic illnesses 2. Cumulative violence exposure and chronic illnesses	IPV and health outcomes among 10y.o	Bullying victimisation/perpetration (BV, BP) and adolescent health
Design	See Table 8	XS study	XS study	Prospective birth cohort study	Secondary analysis of a prospective cohort study
Population		15y.o from all secondary schools in Oslo from 2000 to 2001	Non-institutionalized US households from 2001 to 2004	Mothers giving birth in 6 public hospitals (2003–2005); representative in birth method, birth weight, and gestation	13y.o sampled across South Korea
Sample • ***Size*** • ***Inclusion criteria*** • ***Exclusion criteria***		N = 8316 (88% participation rate) Signed consent from parent/child N.A.	N = 6483 Adolescents < 18y.o Participants with missing data	N = 615 mother/child dyads G1P0 mothers, ≥ 18y.o, ≤ 24 + 0 Participants with missing data	N = 2101 Uses data from baseline assessment (wave 1) and F/U @ 2 (wave 3) and 3y (Wave 4) post.
Exposure (Violence) • ***Violence types*** • ***Positive exposure***	Verbal/Physical/Sexual abuse (1y-prevalence) See Table 6	Physical/Sexual violence; Bullying (1y-prevalence) Positive self-report on National Health Screening of Norway survey ‖	**Lifetime prevalence of:** **Direct violence:** Inflicted onto child **Indirect violence:** Witnessed by child **Any violence:** Direct/Indirect violence **How violence is experienced:** Positive self-report on Composite International Diagnostic Interview **Cumulative violence:** 0, 1, 2, or ≥3 exposures to "Any violence"	**Emotional/Physical IPV (1y prevalence)** Positive maternal report on composite abuse scale; Stratified by timing: **- No IPV** **- Early IPV:** IPV @ 1y and/or 4y **- Recent IPV:** IPV @ 10y	1y prevalence of: - Verbal/Physical BV - Verbal/Physical BP Positive self-report @ wave 3 ¶
Results • ***Outcomes*** • ***Diagnosis criteria*** • ***Adjusted regression analyses***	AD See Table 6 **Verbal abuse and AD:** Positively associated with AD in all three F/Us; **5y:** 1.52 (1.21–1.9) **9y:** 1.45 (1.17–1.78) **15y:** 1.1 (0.87–1.39) **Physical abuse:** Positively associated with AD in all three F/Us: **5y:** 1.36 (1.05–1.76) **9y:** 1.30 (0.94–1.82) **15y:** 1.05 (0.82–1.35) **Sexual abuse and AD:** Non-significant across all three F/Us	AR, AD Positive self–report ¶ **Each violence type and AD/AR** • **Bullying** was positively and significantly associated with AD (aOR: 1.3; 95% CI: 1.1–1.7; $p < 0.05$) in boys only. • **Physical violence** was only positively and significantly associated with AR (aOR: 1.3; 95% CI: 1.1–1.5; $p < 0.05$) and AD (aOR: 1.2; 95% CI: 1.0–1.5; $p < 0.05$) in boys. • **Sexual violence** was only positively and significantly associated with AR (aOR: 1.3; 95% CI: 1.1–1.8; $p < 0.05$) and AD (aOR: 1.4; 95% CI: 1.0–1.9; $p < 0.05$) in girls.	AR Positive self–report (Lifetime prevalence) **Each violence type and AR:** aOR (95% CI) • **Any:** 1.49 (1.19–1.87), $p < 0.05$ • **Direct:** 1.42 (1.01–1.99), $p < 0.05$ • **Indirect:** 1.16 (0.74–1.83), $p > 0.05$ **Cumulative violence and AR:** • **1 event:** 1.37 (0.97–1.95), $p > 0.05$ • **2 events:** 1.91 (1.23–2.98), $p < 0.05$ • **≥3 events:** 1.48 (1.04–2.12), $p < 0.05$	NANIPA Maternal report of physician diagnosis ¶ **IPV and NANIPA:** aOR (95% CI)1.4 (0.8–2.2), $p = 0.24$ **IPV timing and NANIPA:** • **Early exposure:** 1.1, $p > 0.05$ • **Recent exposure:** 1.5, $p > 0.05$	AR Positive self–report (1y–prevalence) **Verbal BV and AR adjusted for demographics only:** • **aOR:** 1.17 • $p <$ 0.01 **Verbal BV and AR adjusted for all other bullying types and demographics:** • **aOR:** 1.17 • $p <$ 0.01 **All other bullying types** were non-significantly associated with AR

Table 7. *Cont.*

	McKenzie et al., 2020, US [9]	Haavet et al., 2004, Oslo [14]	McLaughlin et al., 2016, US [15]	Gartland et al., 2021, Melbourne [16]	Jennings et al., 2017, South Korea [17]
Key findings	1. Except for sexual abuse, exposure to child abuse in the past 1y was positively associated with a 1y-history of AD. 2. This association was highest at 5 years and decreased with age. It was also greater for verbal abuse than for physical abuse 3. At 15 years, association between all child abuse types and AD were non-significant.	1. Exposure to bullying was found... • To have no significant gender differences in prevalence rates • To be significantly and positively associated with AD in boys only. 2. Physical violence exposure • Is significantly more prevalent in boys than girls (29% vs. 16%) • Is significantly and positively associated with AR and AD in boys only. 3. The reverse is true for sexual violence, which is... • Significantly more prevalent in girls than boys (6% vs. 2%) • Significantly and positively associated with AR and AD in girls only.	1. Violence exposure is common, and prevalence significantly rises with age. 2. No gender differences in violence prevalence noted. 3. Positive and significant association between violence and AR was found only for "Any" and "Direct violence". 4. Cumulative violence was found to be significant only for participants reporting $\geq$ 2 violent events.	1. IPV exposure, regardless of timing, is non-significantly associated with increased odds for NANIPA 2. "While the estimates were non-significant for [NANIPA], the consistency in the size and direction of estimates and confidence intervals. . .provide support for potential clinical effects."	1. Verbal BV is the only bullying type to be significantly and positively associated with AR 2. This relationship remained unchanged after adjusting for exposure to other types of bullying.
Limitations	1. All limitations outlined in Table 6 2. Assessment criteria for sexual abuse is highly non-sensitive 3. Exposure criteria for verbal/physical abuse at 15y F/U differs from previous F/Us	1. Covariates adjusted for were unspecified, thus limiting cross-comparability 2. Results not generalisable outside the 15y.o group. 3. Outcome prevalence window was unspecified. If it predates the 1y-prevalence window used for exposure, results may be unsound. 4. Lifestyle factors (e.g., alcohol) were not controlled for and may cause confounding.	1. Lacks cross-comparability as exposure was defined in terms of how violence was experienced. 2. Lifestyle factors (e.g., alcohol) were not controlled for and may cause confounding.	**Selective attrition noted in:** • Younger mothers • Low-income households • Report of IPV • Maternal depression	1. Health outcome not measured at wave 2 and may confound results 2. Ethnocultural differences in disease prevalence and bullying perception may limit cross-comparability. 3. Cyberbullying was unexplored

Results in sub-script are non-significant. $^{||}$: Unvalidated; ¶: Prevalence window unreported.

Table 8. JBI critical appraisal tool for cross-sectional studies.

	Thakur et al., 2020 [10]	**Turney, 2020 [11]**	**Bellis et al., 2018 [12]**	**Feng et al., 2019 [13]**	**Haavet et al., 2004 [14]**	**McLaughlin et al., 2016 [15]**
Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y	Y
Was the exposure measured in a valid and reliable way?	**Valid:** Face-valid **Reliable:** Y	**Valid:** Y **Reliable:** Y	**Valid:** N * **Reliable:** Y	**Valid:** Y **Reliable:** Y	**Valid:** N **Reliable:** Y	Y
Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y	Y
Were confounding factors identified?	Y	Y	Y	Y	Y	Y
Were strategies to deal with confounding factors stated?	Y	Y	Y	Y	N	Y
Were outcomes measured in a valid and reliable way?	**Valid:** Y **Reliable:** Y	N.A.	N.A.	N.A.	N.A.	N.A.
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y

Additional comments: N.A. signifies 'not applicable'; * Two exposures measured.

3.3. Risk of Bias Assessment (Tables 8 and 9)

Of the four cross-sectional studies (2–5 [10–13]) relevant to objective one, two (3 [11], 5 [13]) used fully validated tools to determine exposure status, and only one (2 [10]) used validated diagnostic criteria to ascertain NANIPA status. The remainder relied on child and/or caretaker reports.

The two cross-sectional studies (6 [14], 7 [15]) relevant to objective two relied on adolescent self-reports to determine exposure and outcome status. Only one (7 [15]) used a validated tool to assess for exposure.

The three cohort studies (1 [9], 8 [16], 9 [17]) drew exposed and unexposed patients from similar populations. Each assessed for exposure in a uniform manner, but only one did so with a validated tool. Outcome was determined via caretaker or adolescent reports. All identified and controlled for confounders. Missing data were preserved using multiple imputations.

All studies had clearly outlined eligibility criteria and used appropriate statistical analyses.

Table 9. JBI critical appraisal tool for cohort studies.

	McKenzie et al., 2020 [9]	**Gartland et al., 2021 [16]**	**Jennings et al., 2017 [17]**
Were the 2 groups similar and recruited from the same population?	Y	Y	Y
Were the exposures measured similarly to assign participants to both exposed/unexposed groups?	Y	Y	Y
Was the exposure measured in a valid and reliable way?	**Valid:** N * **Reliable:** Y	**Valid:** Y **Reliable:** Y	**Valid:** Unreported **Reliable:** Y
Were confounders identified?	Y	Y	Y
Were strategies to deal with confounders stated?	Y	Y	Y
Were participants free of the outcome prior to exposure?	Y	Y	N *
Were participants free of the outcome prior to exposure?	N.A.	N.A.	N.A.
Was F/U time reported? Was F/U time sufficient for outcomes to occur?	Y	Y	Y
Was F/U complete? If not, were reasons for attrition described and explored?	N	Y *	N
Were strategies to address incomplete F/U utilised?	Y	Y	Y
Was appropriate statistical analysis used?	Y	Y	Y
Additional comments:	* Unvalidated tool used for determining: (1) Physical child abuse at 15-year F/U; (2) Sexual abuse across all three F/U	* Selective attrition observed for: (1) Younger mothers; (2) Lower family income Report of IPV or maternal depression	* Accounted for in statistical analysis

3.4. Quality Evaluation/Assessment of Certainty

GRADEpro Assessment

All studies were evaluated for quality of evidence using the GRADEpro system, with very low evidence classification being determined for most studies (50%), while moderate was determined for three studies (30%), two were classified as low evidence (20%), and no studies were classified as high-level evidence. The researchers' assessments for each of the criteria covered by the GRADEpro system can be found in Tables 10 and 11, along with their corresponding classifications of the level of evidence.

Table 10. Objective 1.

Author/Year	*Quality Evaluation*					*Level of Quality*
	Risk of Bias	**Inconsistency**	**Indirectness**	**Inaccuracy**	**Other**	
McKenzie and Silverberg, 2020, US [9]	Non-serious	Serious	Non-serious	Serious	None	⊕⊕⊕◯ Moderate
Thakur et al., 2020, US [10]	Serious	Serious	Non-serious	Serious	None	⊕◯◯◯ Very low
Turney, 2020, US [11]	Non-serious	Serious	Non-serious	Serious	None	⊕⊕◯◯ Low
Bellis et al. 2018, Wales [12]	Serious	Very serious	Non-serious	Serious	None	⊕◯◯◯ Very low
Feng et al., 2019, Taiwan [13]	Serious	Very serious	Non-serious	Very serious	None	⊕◯◯◯ Very low

Table 11. Objective 2.

Author/Year	*Quality Evaluation*					*Level of Quality*
	Risk of Bias	**Inconsistency**	**Indirectness**	**Inaccuracy**	**Other**	
McKenzie and Silverberg, 2020, US [9]	Non-serious	Serious	Non-serious	Serious	None	⊕⊕⊕◯ Moderate
Haavet et al., 2004, Oslo [14]	Serious	Very serious	Non-serious	Serious	None	⊕◯◯◯ Very low
McLaughlin et al., 2016, US [15]	Serious	Serious	Non-serious	Non-serious	None	⊕⊕◯◯ Low
Gartland et al., 2021, Melbourne [16]	Non-serious	Serious	Non-serious	Non-serious	None	⊕⊕⊕◯ Moderate
Jennings et al., 2017, South Korea [17]	Serious	Serious	Non-serious	Serious	None	⊕◯◯◯ Very low

4. Discussion

Regarding objective 1, the findings unanimously demonstrate a positive dose-dependent relationship between ACE and NANIPA. The persistence of this trend—albeit at varying significance—across age, ethnicity, and socioeconomic background indicates that the pathophysiological process underpinning this relationship is one that may promote the development of atopy in all children, but to varying degrees. This association, being strongest and of greatest significance in younger children and diminishing with age, also suggests that the timing of exposure is another important factor (1, 3).

There is a growing call for paediatric medicine to integrate trauma-informed care, which is intrinsically linked to an understanding of ACEs and their far-reaching consequences [20]. Most research on the effect of ACEs on development and health has been undertaken in the social sciences, particularly through exploring how different stress-reactive profiles develop as adaptions to their environment [21]. However, building on and amalgamating this body of work with research in paediatric medicine offers a considerably more robust and comprehensive understanding, which can then be used to improve both medical and social care further.

Indeed, there is a growing body of literature surrounding IgE-independent pathways of atopic expression. Of relevance is the link between chronic psychological stress and the immunologic mechanisms of atopy whereby continuous dysregulation of the hypothalamic–pituitary–adrenal axis and the sympathetic–adrenal–medullary system have been associated with an increased susceptibility to atopy [22–24]. This is especially true for

infants and toddlers who are entirely dependent on emotionally engaged nurturance for stress regulation [24,25].

If psychological stress drives atopy, then factors which ameliorate stress may oppose it, as suggested by Bellis and colleagues [12], who reported that "fair treatment" in childhood was associated with lower odds for NANIPA (4). While the findings of a single cross-sectional study are far from conclusive, the wider literature has repeatedly demonstrated the mitigating effects that similar psychosocial factors have on asthma [24,26,27].

Beyond this, little else can be explicated with clarity. Firstly, the extent to which the above may be confounded by the natural progression of IgE-mediated processes is unclear and presents another opportunity for further research.

Secondly, all included studies relied on caretaker and/or self-reports, and bias is another unquantifiable variable—especially so for studies relying on self-reports due to recall bias and childhood amnesia [28]. This problem is mitigated in studies using a 1-year prevalence window. However, this limits both the scope of these studies and their cross-comparability. Further, a 2021 review by Coombes and colleagues [8] reported that children younger than seven are unable to validly self-report health outcomes, and thus, the history is primarily dependent on caretaker reports. Here, the literature becomes mixed with a 2005 review by Brand and Van Dulman [29], ultimately concluding that "we don't know and probably never will" know if a history taken from a parent can be trusted.

Thirdly, the studies lack uniformity in their exposure criteria—a consequence of the present lack of a validated clinical paediatric assessment tool for adversity. This represents a difficult problem to resolve as the multifaceted nature of childhood adversity has created challenges in developing a consensual definition. Further, geographicocultural differences in the types of adversity experienced, their respective prevalence, and how adversity may be perceived, all conspire together to render the data more heterogenous still [30].

The Taiwanese study by Feng and colleagues best exemplifies this (5) [13]. Unlike its Western counterparts, the validated criteria used were developed independently of the 10 ACEs and adopted a much higher threshold for physical abuse for increased specificity.

Turning to objective 2, the findings only become more disparate, with each of the included studies dissecting the relationship between violence and NANIPA in different ways. However, when viewed as a gestalt, several interesting themes emerge.

One would be the diametric sex differences reported by Haavet, Straand, Saugstad and Grünfeld [14]. Such sex differences—although unreported in the other included studies—are congruent with the wider literature which demonstrate that acute psychological stress can also drive atopy by inducing a pro-inflammatory state [31,32]. More high-powered, similarly designed studies are needed to solidify our understanding of the issue.

Another is the finding that only child-experienced violence appears to be significantly associated with NANIPA. While an explanation for this phenomenon could not be found in the literature, it is possible that child-experienced violence may induce a stronger stress response and, thus, a greater hypercortisolic state, which, when repeated, more powerfully drives toxic stress. The negative findings reported in Gartland and colleagues' 2021 [16] multi-centred birth cohort study indirectly support this hypothesis. Here, it was found that IPV—a form of child-witnessed violence—was similarly non-significantly associated with NANIPA.

Lastly, verbal abuse or verbal bullying appears to be the most significant and powerful type of violence associated with atopic dermatitis and rhinitis, respectively (1 [9], 9 [17]). Again, the current dearth of literature investigating childhood adversity and NANIPA precludes the authors from finding an answer. One plausible explanation is that there may be a lower threshold for individuals to perpetuate verbal violence, hence increasing the frequency of psychological stress experienced by the child.

5. Limitations

This review inherited four limitations from the literature.

1. Many of the included studies stratify atopy as "asthma" and "allergies," limiting their contribution to the estimation of the association between adversity and eczema or allergic rhinitis as separate dependent variables and making it impossible to determine if the outcome indeed satisfied the review's criteria.
2. The definitions used for childhood adversity vary tremendously in the literature, making it challenging to perform a search to identify all sources of adversity.
3. Child sexual abuse is challenging to capture, with an estimated 55–70% of victims withholding information until adulthood [33,34]. Further, its highly sensitive nature makes it a topic difficult to explore. Even if asked, the issue of recall bias must be contended with. Thus, the accuracy of the results pertaining to sexual violence in this review must be interpreted with caution.
4. The use of retrospective reporting holds its own limitations, particularly through recall bias and social desirability bias. Although the authors were not able to correct for this, it is proposed that future research be mindful of this potential risk to data reliability and validity. Employing longitudinal methods in future research which actively track development could address this.

The a posteriori decision to modify the eligibility criteria is another limitation. Several steps were taken to minimise the possibility of bias:

1. All changes must be unanimously agreed upon.
2. For every change, the search query would be independently reviewed twice for accuracy.
3. If the search query needed correction, the screening process would be repeated.

In addition, defining ACE as the number of adversity types experienced by the child limits the scope of this review as the review did not search for the duration, frequency, or severity of each individual type of adversity. These are all important aspects of adversity and are thus areas of valuable prospective research.

Lastly, the prevalence for each adversity type fluctuates over time. The most prominent example would be the evolution of the family structure, particularly in the developed world. The United Nations has reported an increasing prevalence of single-parent households and an increasing incidence of divorce in a multitude of countries over the last 50 years [35]. An exposition of how this affects the data from longitudinal studies or retrospective studies looking at the lifetime prevalence of adversity exposure is beyond the scope of this review and is yet another area for research.

6. Future Research and Implications

This study identified interesting and important areas for future research, some of which have been noted in the text above, to encourage and generate more research into these avenues. After all, the mark of good research is that it inspires more good research.

The literature on the relationship between ACEs and NANIPA is underdeveloped, particularly regarding childhood violence exposure and NANIPA, and can greatly benefit from further investigation. Similarly, although this paper highlights the association between the two, the topic can greatly benefit from a more substantial and detailed investigation into underlying psycho-bio-socio mechanisms that underpin these associations.

In addition to the need for future research, the importance of trauma-informed care is becoming exceedingly evident in both research and practice, particularly in the field of paediatrics and child health. By expanding on this literature, particularly through longitudinal studies that tracks the development of allergies over time in children exposed toe ACEs, and through more investigation into the relationship between ACEs and paediatric allergy and immunology, we can better inform our care practices now to improve the future health outcomes.

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Writing—review and editing; Methodology. R.V.: Data curation; Formal analysis. Z.Y.: Writing—review and editing. J.T.: Conceptualisation; Supervision; Methodology; Data curation; Formal analysis. All authors have read and agreed to the published version of the manuscript.

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