The Relationship between Parental Adverse Childhood Experiences and the Health, Wellbeing, and Development Outcomes of their Children: A Systematic Review

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ABSTRACT

Objectives:

A growing body of research is emerging regarding the relationship between parental Adverse Childhood Experiences (ACEs) and negative health, wellbeing, and developmental outcomes in their children. This systematic review seeks to understand the relationship between parental ACEs and the health, wellbeing, and developmental outcomes of their children and whether the relationships differ according to the number and type of parental ACEs.

Method

The review includes articles published between 2000-2021 from studies using quantitative longitudinal methods and multivariate analysis to investigate the relationship between parental ACEs and their offspring's outcomes. Relevant studies were identified through a systematic search of five databases and findings synthesised using a narrative synthesis. This review was registered on PROSPERO (CRD42021274068).

Results

Nineteen studies met the inclusion criteria and were included in the review. This resulted in a combined population sample of 124,043 parents and 128,400 children. Diversity in measurement of parental ACE exposure and in the type of ACEs measured within the studies precluded a meta-analysis. Offspring of parents exposed to ACEs had a higher risk of a range of negative health, wellbeing, and developmental outcomes. This relationship differs according to the number and type of parental ACEs, with a positive relationship observed between the number of parental ACEs and the risk of negative health, wellbeing, and development outcomes in their children.

Conclusions

These findings indicate that screening for parental ACEs by health visitors, midwives and other health or social care staff may identify an at-risk population of infants, children and adolescents and improve child outcomes.

3-6 keywords

Parental Adverse Childhood Experiences; intergenerational; child health; child development.

Introduction

Adverse Childhood Experiences (ACEs) are defined as harmful or distressing childhood events which occur in a child's family or social environment before the age of eighteen[1,2]. It is well recognised that ACEs have a negative long-term impact on health outcomes and behaviours for the individual[1,3–7]. Less is known about the intergenerational effect of parental ACEs exposure. Whilst there is evidence that parental ACEs have a negative impact on their children's health, development, and well-being, no systematic review on this topic has yet been conducted.

Reported prevalence of ACEs varies but approximately one-quarter of people report exposure to one to three ACEs, and around 10% report four or more[8]. Prevalence varies according to classification. The most widely used classification of ACEs is from the original ACE study by Felitti *et al*[9] and is comprised of ten ACEs, categorised into abuse, neglect and household challenges (table 1). More recently, literature[10–13] has argued for the need to expand on the original ACE classification to include additional and more contextual measures such as community violence, peer victimisation, low socioeconomic status and separation from migrant parents. ACE classifications are fluid and likely to change further in the future as research adds to our knowledge of ACEs.

Table 1. The original list of ten ACEs [9]

MAIN CATEGORIES OF ACES	SUB-CATEGORIES OF ACES
Abuse	Physical abuse Sexual abuse Emotional abuse
Neglect	Physical neglect Emotional neglect
Household challenges	Parental substance abuse- *including drugs, alcohol, and smoking* Domestic violence Parental separation/divorce Parental mental health difficulties Parental imprisonment

For the individual, ACEs have a negative long-term impact on health outcomes and behaviours. ACEs have been associated with alcoholism, drug use, smoking-related diseases, coronary heart disease and obesity in adulthood[1,3–6,9,14,15]. It is also known that the more ACEs an individual faces during childhood, the greater the likelihood of negative outcomes[4,6,7,9,16,17].

ACEs affecting a parent may also have consequences for their children. A number of papers have suggested that parental ACEs have a negative impact on their children's health, development, and well-being[2,17,18]. Several mechanisms have been proposed, including: an increased risk of maternal depression in those with ACEs, which in turn is associated with impaired parenting behavioural mechanisms [2,19–21] and an increased risk of prenatal exposure to alcohol or other substances, affecting the healthy development of offspring[21–24]; impaired maternal-infant dyadic functioning[25] or through altered gene expression (epigenetics) [26–28]. Other studies suggest the impact of parental ACEs on the outcomes of their offspring are sensitive to the type and timing of ACE exposure[24,26,29,30].
A multi-generational approach to improve child health outcomes would address both the prevalence of ACEs and the impact of parental ACEs on their children. Antenatal or early childhood screening for parental ACEs may identify children at risk and better target supportive interventions and community health service provision.

This systematic review, to the best of our knowledge, is the first to synthesise evidence from quantitative longitudinal studies to address two questions:

1. What is the relationship between parental ACEs and the health, wellbeing and developmental outcomes of their children (up to the age of eighteen)?
2. Does this relationship differ according to the number and type of parental ACEs?

The review focussed on the ten original ACEs (table 1). This is because this review is looking at previous publications, the vast majority of which use this widely accepted classification.

METHODS

We conducted this review in accordance with the 'Preferred Reporting in Systematic Reviews and Meta-Analysis' (PRISMA) guidelines[31,32], and utilised narrative synthesis[33]. This review was registered on the PROSPERO database (registration number: CRD42021274068)[31,32].

Eligibility Criteria

Inclusion and exclusion criteria are detailed in Table 2. There was no language exclusion but the review was restricted to quantitative longitudinal studies to provide understanding regarding the strength, direction and size of relationships, and to papers employing multivariate analysis in which maternal age, parental education and other variables affecting child outcomes were controlled for.

Table 2. Criteria for inclusion or exclusion of studies.

	INCLUSION CRITERIA	EXCLUSION CRITERIA
FOCUS	Papers focussing on the impact of parental ACEs on offspring's development, health and socioeconomic outcomes	Papers focussing on the impact of ACEs on the individual's own subsequent health, wellbeing and development outcomes
EXPOSURE OF INTEREST	Papers that have explored the impact of having at least one parent who has experienced at least one ACE, on offspring's outcomes	NA
METHODOLOGY	Quantitative design Longitudinal design Multivariate analyses	• Qualitative design • Cross-sectional • Descriptive/bivariate analyses only
DATE	Publication date of 2000-2022	Publication date of earlier than 2000
SETTING	Global literature	N/A
TYPE OF PUBLICATION	Academic peer-reviewed published articles describing primary research	• Publications that are not peer-reviewed • Reviews • Editorials • Letters • PhD theses

Search Strategy

Seven broad categories of outcomes were selected for investigation following a scoping search of over 50,000 papers. Database search terms were constructed around these concepts and combined with the Boolean operator "AND". The search strategy was tested in Medline then expanded to CINAHL, PsycINFO, SocINDEX and Academic Search Ultimate. Databases were searched up to the

31st January 2022. The search strategy in all databases was limited to studies published between 2000-2022. The bibliography and reference lists of all relevant studies were searched for additional relevant studies. The Medline search strategy is presented in Appendix 1.

Selection process

Screening consisted of title, abstract and full-text screening. Two reviewers (RA and FA) screened half of the study titles independently identifying studies as relevant, irrelevant or 'unsure' based on the title indicating the study examined the impact of parental ACEs on offspring's outcomes, or not. The 'unsure' category was then re-screened into either the relevant or irrelevant group. Both reviewers independently reviewed the abstracts of studies identified as relevant from the title screening process and determined their relevance. The full text of all potentially relevant studies was screened by RA against the inclusion and exclusion criteria (Table 2). Where relevancy was unclear, the second reviewer was consulted.

Data Collection Process

RA independently extracted data using the JBI Manual for Evidence Synthesis guidance[34]. Data relevant to the study characteristics (author, year, journal and aim), study design, subject characteristics, exposure, outcome and independent variables, and key findings, were extracted into a Microsoft Excel Spreadsheet[35].

Critical Appraisal

Quality of individual studies was assessed using the Critical Appraisal Skills Programme (CASP) checklist for cohort studies[36], where a study's maximum score was 24. Although there is no agreed way of summarising the scores for the CASP tool, we followed Njau *et al*[37] (where a total score of ≥20 = high quality; 16-19 = moderate quality; ≤15 low quality) and reviewed each of the individual quality items to support the analysis and data synthesis process. Quality was screened by RA and double-screened by PH and FA. See Appendix 5 for the CASP critical appraisal of included studies.

Data synthesis

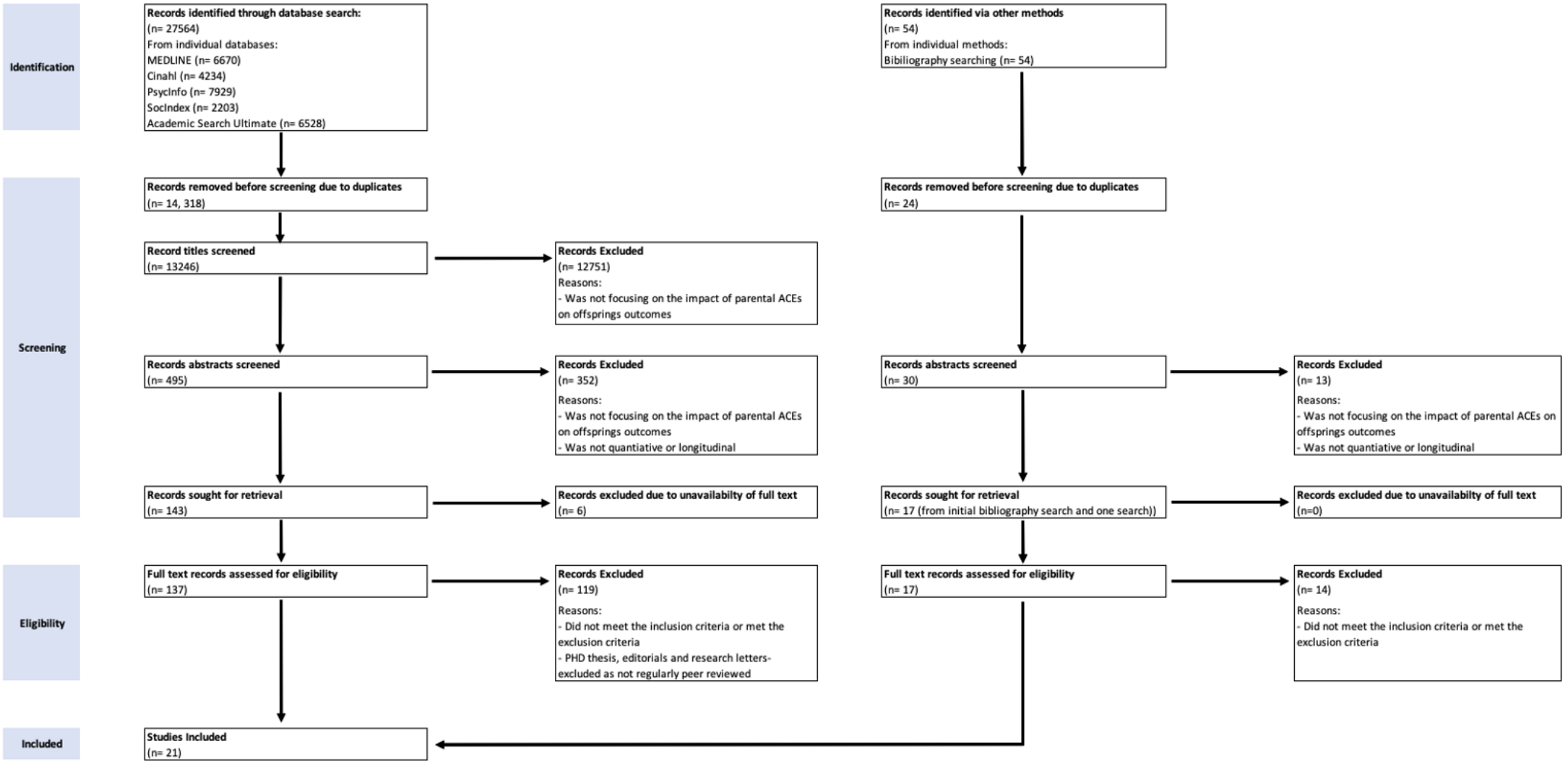
Meta-analysis was precluded due to methodological diversity within the studies, including diversity in the range of outcomes reported, the age at which the outcomes were assessed, and the type of ACEs studied. A narrative synthesis was conducted using the Cochranes guidance on narrative synthesis[33]. First, included studies were grouped and analysed by outcome category measure, exploring findings related to review question one. Outcome categories were defined by reviewer one to ensure replicability:

- **Cognitive development** was defined as the development of knowledge, skills, problem-solving, perception and language[38].
- **Childhood growth outcomes** related to the growth of the offspring, such as preterm delivery and low birth weight.
- **Emotional development** was defined as how children notice, express, and manage emotions[39].
- **Risk-taking behaviour** outcomes were defined as any conscious or unconscious actions where there is uncertainty surrounding the outcome, such as smoking, drug use, and risky sexual behaviour[40].

- **Receipt of child protection support/social work intervention** was defined as measures and structures put in place to prevent and respond to child abuse, neglect, exploitation, and violence[41].
- The definitions of **physical and mental health** outcomes, and **educational attainment**, were determined to be implicit, including illnesses such as obesity, depression, and anxiety[42], and outcomes relating to children's learning.

Next, studies that investigated associations specific to the number or type of ACEs were grouped to answer the second review question. Studies were sorted according to whether they were investigating how the number and/or the type of ACEs impacts the relationship between parental ACE and offspring health, wellbeing, and developmental outcomes. Findings were compared within the sub-groups, but when making comparisons, reviewer one considered the ACE measure used and outcomes explored.

Figure 1: PRISMA flow diagram of ACE review



Adapted from: Page *et al*[31]; Page *et al*(B)[32].

RESULTS

Characteristics of Included Studies

An overview of the characteristics of included studies can be viewed in table 3. A more detailed description can be seen in appendix 2.

Setting

The 21 studies included in this review were published between 2007 and 2022 (see figure 1), and scored high quality on the CASP (Appendix 2 and Appendix 5). Most (n=14) were conducted in the USA[17,43–55]. Three studies were conducted in the UK[56–58] and in Canada[59–61] and one (5.3%) in Norway[62]. None were conducted in low- or middle-income countries.

Participants

Most studies (n=18) included mother-infant dyads exclusively, with only three studies also including father-infant dyads[17,46,59]. Age of the offspring when outcomes were investigated ranged from birth[44,48–50] to eighteen years of age[59]. Prevalence in the parent population of exposure to at least one type of ACE during childhood ranged from 17.1%[57] to 68.2%[59].

Study Design

All studies, apart from Noll *et al*[50], collected ACE exposure data retrospectively using questionnaires, most commonly using the Original ACE Questionnaire[15,17,44,46,47,51,59–61,63] and the Childhood Trauma Questionnaire[48,49,52,53,56,64]. Noll *et al*[50] collected ACE data prospectively, identifying young girls who had reported exposure to sexual abuse to child protection services in the last six months and following them through until motherhood. The average number of types of ACEs examined was 5.2, with the range of 1-10. Sexual abuse (95.2%) and physical abuse (90.5%) were the two most common type of ACEs investigated, with parental imprisonment being the least common (28.6%).

Emotional development was the most common outcome category investigated (n=10) followed by physical and mental health (n=6), cognitive development (n=3), risk-taking behaviours (n=2), childhood growth (n=2) and educational attainment (n=1). No studies were included that investigated the outcome category of receipt of child protection support.

Table 3. Overview of included studies

	Studies (n)	Studies %
ACE measured		
Sexual abuse	20	95.2
Physical abuse	19	90.5
Emotional abuse	13	61.9
Physical neglect	10	47.6
Emotional neglect	10	47.6
Parental separation/divorce	9	42.9
Domestic Violence	9	42.9
Parental substance abuse	8	38.1
Parental mental health difficulties	8	38.1
Parental imprisonment	6	28.6
Scales to measure ACEs		
Original ACE Questionnaire	8	38.1
Childhood Trauma Questionnaire	5	23.8
Traumatic Life Events Questionnaire	3	14.3
Unvalidated measure	2	9.5
Norvold Abuse Questionnaire	1	4.8
Trauma History Questionnaire	1	4.8
Prospective measure	1	4.8
Country study was conducted in		
USA	14	66.7
UK	3	14.3
Canada	3	14.3
Norway	1	4.8
Outcome category investigated		
Emotional development	10	47.6
Physical/mental health	6	28.6
Cognitive development	3	14.3
Risk-taking behaviours	2	9.5
Childhood growth	2	9.5
Educational attainment	1	4.8
Receipt of child protection support	0	0.0
Setting		
Large diverse population	8	38.1
Urban	8	38.1
Other / unspecified	4	19
Low-income	2	14.3

Critical Appraisal Skills Programme (CASP) overall rating		
High quality	20	95
Moderate quality	1	5
Low quality	0	0

Review question 1: What is the relationship between parental ACEs and the health, wellbeing, and developmental outcomes of their offspring (up to the age of 18)?

Cognitive development

Three studies explored the association between parental ACE exposure and offspring cognitive development outcomes[17,48,49]. Folger *et al*[17] found for each additional maternal ACE reported, there was an 18% increase in the risk of suspected developmental delay in communication, fine and gross motor skills, personal-social function and problem-solving at age 2 (RR= 1.18, 95%CI (1.08-1.29)). Mothers who reported at least 3 ACEs were 2.23 times more likely to have a child with a suspected developmental delay. Hendrix *et al*[48] found that maternal emotional abuse was significantly associated with stronger functioning coupling between the amygdala and the medial prefrontal cortex. This accelerated development can increase risk for certain neuropsychiatric disorders[65] and decrease neural plasticity[66,67]. Moog *et al*[49] observed a significant association between maternal childhood abuse or neglect and new-born grey matter volume. These studies indicate that maternal childhood experiences of abuse and neglect can negatively affect the cognitive development of offspring through impaired brain development and suspected developmental delay.

Childhood growth

Two studies explored the association between parental ACE exposure and offspring growth[44,50]. Noll *et al*[50] found offspring of mothers who had been sexually abused in childhood were 2.8 times more likely to be born preterm (OR: 2.8±1.44, 95%CI= ±0.37, $p<0.05$). Ciciolla *et al*[44] found infants of mothers with exposure to 6 ACEs were four times more likely to be born preterm, have a low birthweight or be admitted to a new-born intensive care unit (NICU) during the first 6 weeks (OR= 4.33, 95% CI (1.02, 18.39). When investigated as a separate outcome, infants of mothers with high ACE exposure were almost nine times more likely to be admitted to NICU (OR= 8.7, 95%CI (1.34, 56.65).

Physical and mental health

Five studies explored the association between parental ACE exposure and offspring physical health outcomes[43,46,52,53,59]. None examined mental health outcomes in children.

Children of mothers exposed to childhood physical, sexual and emotional abuse, or domestic violence were significantly more likely to be either overweight or obese[52], or diagnosed as autistic by age 3[53], and at increased risk of infant bronchiolitis diagnosis after adjusting for maternal smoking, asthma and social support[43]. Beveridge *et al*[59] found parental ACE exposure was not a significant predictor of youth pain intensity, but did predict parent chronic pain status. Eismann *et al*[46] found higher maternal exposure to ACEs was significantly associated with an increased risk of missed well-child visits (routine check-ups) by age 2. For each additional maternal ACE exposure, there was a 12% increased incidence rate of missed well-child visits (OR= 1.12, 95%CI (1.03, 1.22)).

These studies indicate that maternal ACEs can negatively impact the physical health outcomes of their offspring and early use of health care.

Emotional Development

Seven studies[45,47,54,56,58,60,61] examined the association between parental ACEs and their children's internalising behaviour, specifically emotion disorder, anxiety, depression, somatisation, separation anxiety and peer problems. Five studies found a small but significant association[45,54,56,58,61] and two found a non-significant but trending association[48,60] between maternal ACEs and offspring internalising behaviour. Fenerci and Allen[45] found that there was a positive association between maternal childhood experience of physical abuse and domestic violence, but not sexual abuse. Interestingly, the two studies that found evidence of a lack of association, were the only two to use all ten maternal ACEs as exposure variables in their analysis, collected through the Original ACE Questionnaire. This suggests it is plausible that only specific types of maternal ACEs may be a risk factor for offspring's internalising behaviour, and that the association is diluted due to the inclusion of other, unrelated maternal ACEs in these studies.

Seven studies[45,47,56,58,60–62] observed a significant association between maternal ACEs and children's externalising behaviour (hyperactivity, aggression, disruptive behaviour disorder and conduct problems). Fenerci and Allen[45], the only study to explore the associations between specific types of ACEs and offspring externalising behaviours at 12 years of age, observed a significant association with physical, but not sexual, abuse.

Other studies observed a significant association between maternal ACEs and surgency/extraversion temperament and/or negative affectivity[61]; maternal childhood sexual abuse and oppositional, peer and conduct problems[55]; and maternal physical, sexual, and emotional abuse and their children's adjustment problems at age 4 and 7 (parent-reported adjustment)[57].

These studies suggest that maternal ACEs can negatively impact the emotional development outcomes of their offspring. Impaired emotional development can have significant implications on the health, wellbeing and developmental outcomes of the child, such as through poor educational attainment and later psychopathology.

Educational Attainment

One study explored the association between maternal childhood sexual abuse and educational attainment of offspring up to age 7[55], observing that children of mothers with a history of childhood sexual abuse had significantly lower scores on picture vocabulary tests used to assess expressive language skills, compared to children of mothers with no history of childhood sexual abuse.

Risk-taking behaviours

Two studies investigated the relationship between parental ACEs and offspring's smoking[51,52]. Pear *et al*[51] found a maternal childhood history of physical abuse and parental substance abuse was significantly associated with a 20% and 17% increased risk level of offspring smoking, respectively. Roberts *et al*[52] reported that mothers' exposure to childhood abuse was a significant predictor of her offspring smoking. Additionally, offspring of mothers who reported the most severe level of childhood abuse were at the greatest risk of smoking.

Review question 2: Does this relationship differ according to the number and type of parental ACEs?

Eight studies included in the review investigated how the observed association between parental ACEs and offspring outcome differed according to the number of ACEs the parent was exposed to; all observed an increase in the number of parental ACEs increased the risk to the offspring of

experiencing a negative outcome in their cognitive development[17,48,49], physical health[43,46,53] or emotional development[47,57].

Seven studies investigated how the relationship differed according to the type of parental ACEs[48,51–53,56,57]. Five, with the exception of Collishaw *et al*[57] and Myhre *et al*[62], found that the associations observed between overall ACE score and offspring outcomes differed when specific ACE types were examined. For example, maternal childhood physical and emotional, but not sexual, abuse were risk factors of offspring's autism diagnosis[53]. Pear *et al* [51] found that a mother's experience of parental mental illness in her childhood was not associated with her offspring smoking, but maternal childhood physical abuse and parental substance abuse during her childhood, was.

DISCUSSION

To our knowledge, this is the first systematic review to examine the relationship between parental ACEs and the health, wellbeing, and developmental outcomes of their children. Significant associations were observed between parental ACEs and offspring outcomes, with the exception of offspring pain intensity. When parents were exposed to ACEs, their children were significantly more likely to have impaired brain development, developmental delay and learning difficulties; be born preterm; be more likely to be diagnosed with bronchiolitis, obesity, or autism; miss routine health check-ups; demonstrate externalising behaviours or a sub-optimal temperament (defined as extraversion or negative affectivity); have adjustment or socioemotional development problems; and smoke. Overall findings suggest that parental exposure to ACEs negatively impact the health, wellbeing, and developmental outcomes of their offspring. It is possible that the impact of parental ACEs on child health, well-being, and development extends beyond the outcomes examined in the studies included in this review.

A consistent finding was that, as the number of ACEs a parent was exposed to increased, the greater the negative effect on their children, indicating that children of parents who experienced many ACEs are more at risk of negative health, wellbeing, and developmental outcomes. The studies also suggest the relationship between parental ACEs and offspring outcome is type dependent, although inconsistency in the outcomes studied precludes reaching a clear understanding of which types of parental ACEs pose a greater risk to children's health, wellbeing, and development outcomes. Overall, the results indicate that the relationship between parental ACEs and offspring outcomes, differs according to the number and type of parental ACEs.

Policy and practice implications

These findings support interventions aimed at reducing the occurrence of ACEs and underpin the need to take a 'multi-generational' approach in addressing the effects of ACEs. A conventional method used by front-line health and other community workers to identify children at risk is to examine the child's environmental, sociodemographic, or economic characteristics. Whilst this review does not provide evidence against this method of identification, it suggests screening for parental ACEs might lead to earlier identification of potentially at-risk children and enable community teams to more accurately target interventions for children at risk of negative health, wellbeing, and developmental outcomes. The design and delivery of interventions may also be better informed and bespoke, in response to ACE-related information. Additionally, evidence that babies of mothers who were exposed to ACEs had a significantly higher risk of being born preterm and/or with impaired brain development[44,48–50] indicates that screening for parental ACEs should be conducted early in pregnancy, if interventions implemented prior to birth can reduce this risk. The

included studies indicated some mediating variables between parental ACEs and offspring outcomes, such as maternal physical and mental health, smoking and alcohol use and offspring and maternal telomere length. This is another important avenue for further investigation.

Limitations

Criteria for classifying ACEs have been debated since Felitti *et al's*[9] initial work in this area. However, in order to conduct a systematic review of the literature it was necessary to use a focused classification of ACEs. As the ten categories of ACEs described by Felitti *et al*[9] are the most widely used classification of ACEs, they were the focus of our review. This may have excluded studies that use other classifications of ACEs.

Methodological limitations within the included papers reduced the ability to draw firm conclusions. They included mostly retrospective examination of parental ACEs, variability in the methods used to measure parental ACE exposure and type and number of ACEs measured, lack of continuity over the age at which a child's outcomes were investigated, and a lack of studies investigating child outcomes past the age of thirteen. This diversity precluded a meta-analysis.

All studies were conducted in high-income countries, limiting the generalisability of findings to middle- and low-income countries, or to humanitarian settings where the population may have greater exposure to ACEs. This disparity may have been exacerbated by the inclusion only of (expensive) longitudinal studies.

Some studies included in this review used data from pre-existing cohorts. Four pre-existing cohorts were used in more than one study, and it is possible that the data from individual patients may have been used more than once. Whilst this has the potential to introduce bias, the narrative synthesis approach of this review will limit the potential for any bias.

Within a systematic review it is possible to define the search terms used both narrowly and widely. Defining the search term widely will inflate the number of papers identified and it is important to maintain a focus consistent with the scope of the research question. The search terms we used identified over thirteen thousand unique papers, which were manually screened by the authors. It is possible that in the area of defining 'parental mental health difficulties', too narrow an approach was taken. However, during an initial scoping exercise it was found that widening this term led to inclusion of a large number of papers outside of the scope: in particular those concerning maternal depression during pregnancy. We therefore believe our focused approach allowed us to explore the comprehensive literature on the topic, within the scope of our review.

Recommendations for future research

A notable research gap is the effect of paternal ACEs on offspring outcomes. Only two of the nineteen studies included fathers in their population sample, and even in these studies, a smaller number of fathers participated than mothers.

Secondly, no studies investigated outcomes beyond age 13. Following up children to at least the age of eighteen would increase the number of studies investigating outcomes such as receipt of child protection support, mental health outcomes or educational attainment, which were largely unexplored.

Thirdly, the lack of studies conducted in low- or middle-income countries and humanitarian settings is an important gap, since parental resilience to provide protective and nurturing care may come under strain. Further research using current tools or contextually modified ACEs that better reflect

adversities in those settings, may enable better targeting of limited resources on infants and households most at risk in populations experiencing widespread acute need.

Fourthly, more research is needed to investigate the association between maternal ACEs and offspring internalising behaviour, with types of ACEs separated to measure specific effects, before forming a conclusive statement regarding the association**.**

Finally, seeking agreement on definitions of ACEs and outcomes of particular interest would allow collaboration across longitudinal studies, creating a valuable resource to increase the potential from future research investigating the relationship between parental ACEs and offspring outcomes. Future research, including primary research, should be conducted to examine impact of specific types of ACEs, including wider definitions as proposed by Cronholm *et al*[68] and Finkelhor *et al*[69].

CONCLUSION

Findings suggest that offspring of parents who have been exposed to ACEs are at greater risk of a variety of negative health, wellbeing and developmental outcomes. Additionally, this relationship differs with the number and type of parental ACE exposures, with a positive relationship being observed between the number of parental ACEs and risk of negative outcomes in their offspring. These findings have implications for policy and practice, including the recommendation that screening for parental ACEs by health or community workers may be an effective way to identify at-risk infants, children and adolescents, enabling earlier or bespoke interventions. Overall, this review provides a comprehensive overview of available literature on this relationship and highlights the important implications that accounting for parental ACEs may have towards efforts to improve child outcomes.

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Appendix 1: Table of the phrases used to search for relevant terms

POPULATION:	
PARENTS, CHILD-PARENT RELATIONS	(MH ("Parenting" OR "Parent-Child Relations+")) OR (TI ((intergen* OR inter-gen* OR offspring OR child* Or son* OR daughter* OR parent* OR maternal OR paternal Or parental OR mother* OR father* OR dad* OR mum* OR mom* OR guardian*) N5 (outcome* OR associat* OR risk OR impact* OR effect* OR link* OR relate* OR predict* OR affect* OR relation* OR relate* OR confer OR continuity OR role OR contribut* OR concordance OR influence* OR likel* OR transmi*)) OR AB ((intergen* OR inter-gen* OR offspring OR child* Or son* OR daughter* OR parent* OR maternal OR paternal Or parental OR mother* OR father* OR dad* OR mum* OR mom* OR guardian*) N5 (outcome* OR associat* OR risk OR impact* OR effect* OR link* OR relate* OR predict* OR affect* OR relation* OR relate* OR confer OR continuity OR role OR contribut* OR concordance OR influence* OR likel* OR transmi*))))
AND	
EXPOSURE:	(MH ("ADVERSE childhood experiences" OR "ADVERSE childhood experience") OR (TI ("Adverse Childhood Experience*" OR "ACE" OR "ACEs") OR AB ("Adverse Childhood Experience*" OR "ACE" OR "ACEs") OR TI ((child*) N5 ((physical* OR emotional* OR sexual* OR verbal* OR psychological*) N2 (abuse* OR neglect* OR trauma* OR maltreat* OR violence) OR adversity OR "impair* parent")) OR AB ((child*) N5 ((physical* OR emotional* OR sexual* OR verbal* OR psychological*) N2 (abuse* OR neglect* OR trauma* OR maltreat* OR violence) OR adversity OR "impair* parent")) OR TI ((parent*) N5 ((separat* OR divorce*) OR ((mental*) N2 ("health difficulties" OR "ill health" OR ill)))) OR AB ((parent*) N5 ((separat* OR divorce*) OR ((mental*) N2 ("health difficulties" OR "ill health" OR ill)))) OR TI ((parent*) N5 ((substance OR drug OR alcohol OR tobacco OR smoke* OR nicotine OR drink*) N2 (use* OR abuse* OR misuse* OR addict*))) OR AB ((parent*) N5 ((substance OR drug OR alcohol OR tobacco OR smoke* OR nicotine OR drink*) N2 (use* OR abuse* OR misuse* OR addict*))) OR TI ((parent*) N5 ("binge drink*" OR alcohol* OR ((domestic OR partner OR "intimate partner") N2 (violence OR abuse)) OR abuse*)) OR AB ((parent*) N5 ("binge drink*" OR alcohol* OR ((domestic OR partner OR "intimate partner") N2 (violence OR abuse)) OR abuse*))))
AND	
OUTCOME:	((MH "Cognitive Dysfunction") OR (MH "Infant Health") OR (MH "Child Health") OR (MH "Adolescent Health") OR (MH "Infant, Premature") OR (MH "Infant, Low Birth Weight") OR (MH "Infant, Extremely Premature") OR (MH "Child Development") OR (MH "Adolescent Development") OR (MH "Education") OR (MH "Child Protective Services")) OR TI ((infant* OR baby* OR newborn* OR child* OR adolescent* OR teen* OR offspring OR youth) N5 (development OR "cognitive development" OR "cognitive learning" OR "cognitive dysfunction" OR learning OR function* growth OR premature OR preterm OR "birth weight" OR "birth outcome"))) OR AB ((infant* OR baby* OR newborn* OR child* OR childhood OR adolescent* OR teen* OR offspring OR youth) N5 (development OR "cognitive development" OR "cognitive learning" OR "cognitive dysfunction" OR learning OR function*)) OR AB ((infant* OR baby* OR newborn* OR child* OR childhood OR adolescent* OR teen* OR offspring OR youth) N5 (health OR development* OR adversity OR outcome* OR risk OR burden OR risk OR "risk taking" OR "risk-taking")) OR TI ((infant* OR baby* OR newborn* OR child* OR childhood OR adolescent* OR teen* OR offspring OR youth) N5 (health OR development* OR adversity OR outcome* OR risk OR "risk taking" OR "risk-taking")) OR AB ((infant* OR baby* OR newborn* OR child* OR childhood OR adolescent* OR teen* OR offspring OR youth) N5 (education* OR "education* attainment" OR "education* outcome*") OR TI ((infant* OR baby* OR newborn* OR child* OR childhood OR adolescent* OR teen* OR offspring OR youth) N5 (education* OR "education* attainment" OR "education* outcome*") OR AB ((infant* OR baby* OR newborn* OR child* OR childhood OR adolescent* OR teen* OR offspring OR youth) N5 ("child protection" OR "child protection services" OR "child protection support" OR "social work" OR "child protection intervention" OR "social work intervention" OR "social work intervention*" OR "child protection intervention*") OR TI ((infant* OR baby* OR newborn* OR child* OR childhood OR adolescent* OR teen* OR offspring OR youth) N5 ("child protection" OR "child protection services" OR "child protection support" OR "social work" OR "child protection intervention" OR "social work intervention" OR "social work intervention*" OR "child protection intervention*")))
AND	
STUDY DESIGN:	(MH ("quantitative research" OR "quantitative study" OR "quantitative method*" OR quantitative OR "Cohort Studies" OR "Surveys and Questionnaires" OR "Longitudinal Studies" OR "Follow-Up Studies") OR TI (quantitative OR statistics OR "numerical data" OR assessment OR cohort OR ((quantitative) N2 (study OR design OR research OR method))) OR AB (quantitative OR statistics OR "numerical data" OR assessment OR cohort OR ((quantitative) N2 (study OR design OR research OR method))) OR TI (survey* OR questionnaire* OR measure* OR (("ACE" OR "ACEs" OR "adverse childhood experience*") N3 (measure*))) OR AB (survey* OR questionnaire* OR measure* OR (("ACE" OR "ACEs" OR "adverse childhood experience*") N3 (measure*))) OR TI (longitude* OR longitudinal OR "follow* up" OR "follow*-up" OR "time points" OR "time-points" OR "long term" OR ((longitude OR longitudinal) N2 (study OR studies OR design OR research OR method*))) OR AB (longitude* OR longitudinal OR "follow* up" OR "follow*-up" OR "time points" OR "time-points" OR "long term" OR ((longitude OR longitudinal) N2 (study OR studies OR design OR research OR method*)))
QUANTITATIVE, LONGITUDINAL, FOLLOW-UP, COHORT, SURVEYS AND QUESTIONNAIRES	

*MeSH term = MH

Appendix 2: Characteristics of included studies

Study	Country and setting	Data source and year(s) *	Population	ACEs measured (n, max=10)	Exposure Variable	% of population with 1 ACE (%)	Outcome category reported. All specific outcomes explored are in parentheses.	Main findings related to specific outcome(s)	Total quality score (n/24) **
Adgent et al[43]	USA-urban poverty setting	Data source: Urban Child Institute CANDLE study[70] Years: 2006-2011	639 mother-infant dyads Predominantly low-income, African American population	3	Physical abuse, Sexual abuse, and Domestic Violence *Measured: Traumatic Life Events Questionnaire*[71]	42	Physical/mental health conditions/ disorders *(Infant bronchiolitis)*	Increasing number of maternal childhood traumatic events associated with an increased risk of infant bronchiolitis. No change in risk for an offspring of a mother who reported exposure to one ACE versus offspring of a mother who reported exposure to none, however, adjusted risk ratios increased with reports of exposure to two ACEs (RR= 1.31, 95%CI (0.83, 2.07)) and three ACEs (RR=2.65, 95% CI (1.45, 4.85))	20
Beveridge et al[59]	Canada-Clinical sample of youth with chronic pain taken from tertiary-level outpatient chronic pain clinics at paediatri	Data Source: Pain and Mental Health in Youth (PATH) Study[72]	192 parent-child dyads All children had reported chronic pain	10	Physical abuse, Sexual abuse, Emotional abuse, Physical neglect, Emotional neglect, Domestic Violence, Parental substance abuse, Domestic Violence, Parental separation/divorce, Parental mental health difficulties and Parental imprisonment *Measured: Original ACE Questionnaire* [73]	68.2	Physical/mental health conditions/ disorders *(Youth chronic pain intensity)*	Parental ACE score was not a significant independent predictor of youth pain intensity or youth pain interference (beta=0.07, p=0.383). Parental ACE score was a significant independent predictor of parent chronic pain status (OR= 1.19, 95% CI (1.01, 1.4)).	19

	c hospitals							
Choi et al[56]	UK- twin population-based sample	Data source: Environmental Risk (E-Risk) Longitudinal Twin Study[74] Years: Tracked twins born between 1994-1995	1016 mothers-twin infant dyads	6 (plus 3 extra)	Physical abuse, Sexual abuse, Emotional Abuse, Physical neglect, Emotional neglect and Parental Separation As well as: death of a family member, a victim of community violence and personal illness *Measured: Childhood Trauma Questionnaire*[75]	24	Emotional Development *(Internalising behaviour and externalising behaviour)*	**Internalising behaviour:** Maternal childhood maltreatment significantly associated with offspring internalising behaviour (beta=0.33, p<0.001) **Externalising behaviour:** Maternal childhood maltreatment significantly associated with offspring externalising behaviour (beta=0.35, p<0.01)	22
Ciciolla et al[44]	USA- low income urban populations	Primary data collected specifically for study	124 mother-infant dyads	10	Physical abuse, Sexual abuse, Emotional abuse, Physical neglect, Emotional neglect, Domestic Violence, Parental substance abuse, Domestic Violence, Parental separation/divorce, Parental mental health difficulties and Parental imprisonment *Measured: Original ACE Questionnaire* [73]	NA Low ACEs (0-2) = 56.1% Moderate ACEs (3-5) = 26.2% High ACEs (6+) = 17.7%	Childhood growth and physical/mental health disorders (*Preterm birth, low birth weight and NICU hospitalisation*)	**Adverse infant outcome (Preterm birth, low birth weight and NICU hospitalisation):** Women with higher ACEs (6+) had 4 times the odds of reporting an adverse infant outcome (OR = 4.33, 95% CI (1.02, 18.39) **NICU hospitalisation:** Women with higher ACEs (6+) had almost 9 times the odds of a NICU hospitalisation (OR= 8.7, 95% CI (1.34, 56.65) Mothers ACE scores pose a significant risk for infant health outcomes	21
Collishaw et al[57]	UK- population based sample	Data Source: Avon Longitudinal Study of Parents and Children (ALSPAC)[76]	5619 mother-infant dyads	3	Physical abuse, Sexual abuse, and Emotional abuse *Measured: Traumatic Life Events questionnaire* [71]	17.1	Emotional Development *(Offspring adjustment)*	All forms of abuse investigated were significantly associated with increased offspring adjustment problems at 4 and 7 years of age. Significantly higher adjustment problems for more severe reports of maternal childhood abuse	23

		Years: 1991-1994							
Eismann et al[46]	USA-urban setting, possibly more affluent population	Primary data collected specifically for study	515 parent-infant dyads (374 mothers, 156 fathers) 156 mothers and fathers both involved	10	Physical abuse, Sexual abuse, Emotional abuse, Physical neglect, Emotional neglect, Domestic Violence, Parental substance abuse, Domestic Violence, Parental separation/divorce, Parental mental health difficulties and Parental imprisonment *Measured: Original ACE Questionnaire* [73]	Mothers: 48.7 Fathers: 47.4	Physical/mental health conditions/ disorders *(Missed well-child visits, sick visits and immunisation completion)*	Maternal ACE exposure was significantly associated with an increased risk for missed well-child visits (routine check-ups) by 2 years of age (OR=1.12, 95%CI (1.03, 1.22)). No associations were observed between maternal ACEs and sick visits or immunisation completion, or paternal ACEs and any of the offspring outcomes	21
Esteves et al[47]	USA	Primary data collected specifically for study	155 mother-infant dyads	10	Physical abuse, Sexual abuse, Emotional abuse, Physical neglect, Emotional neglect, Domestic Violence, Parental substance abuse, Parental separation/divorce, Parental mental health difficulties and Parental imprisonment *Measured: Original ACE Questionnaire* [73]	NA (mean score = 2.29)	Emotional Development *(Internalising behaviour and externalising behaviour)*	**Internalising behaviour:** Maternal ACE exposure not significantly associated with internalising behaviour (β=0.650, 95%CI (-0.211, 1.511), p=0.14) **Externalising behaviour**: Maternal ACE exposure significantly associated with higher externalising behaviour problems in offspring at 18 months (β=1.528, 95%CI (0.562, 2.495), p=0.002)	23
Fenerci and Allen[45]	USA-population based setting	Data Source: Longitudinal studies of child abuse and neglect (LONGSCAN)[77]	706 mother-infant dyads Study of women and their children with either a history of or at risk of maltreatment	2	Physical abuse and Sexual abuse *Measured: Caregiver's History of Loss and Victimization (VICA) (unvalidated measure)*	NA (sexual abuse= 38.2, physical abuse= 34.3)	Emotional Development *(Internalising behaviour and externalising behaviour)*	**Internalising behaviour:** Higher levels of maternal childhood physical abuse significantly predicted internalising behaviours at age of 12 (p<0.001), however no association with maternal childhood sexual abuse and self-reports of internalising behaviour **Externalising behaviour:** Higher levels of maternal childhood physical abuse significantly predicted externalising behaviours in offspring at age of 12 (p<0.001), however no association with	20

								maternal sexual abuse and self-reports of externalising behaviour	
Folger et al[17]	USA-urban setting	Primary data collected specifically for study	311 mother-infant dyads, 122 father-infant dyads. Of these, 100 parent-infant dyads (ACE information from both mother and father)	10	Physical abuse, Sexual abuse, Emotional abuse, Physical neglect, Emotional neglect, Domestic Violence, Parental substance abuse, Parental separation/divorce, Parental mental health difficulties and Parental imprisonment *Measured: Original ACE Questionnaire* [73]	Mothers: 47.9 Fathers: 47.5	Cognitive development *(Developmental status)*	Exposure of mothers and fathers to ACEs resulted in an increased risk of suspected developmental delay in their offspring (maternal ACEs: RR: 1.18, 95%CI (1.08–1.29). Paternal ACEs: RR: 1.34, 95%CI (1.07–1.67)) An increase in the number of ACEs during childhood associated with a higher risk of suspected developmental delay in offspring	21
Hendrix et al[48]	USA-urban setting	Data Source: Emory University African American Vaginal, Oral and Gut Microbiome in Pregnancy Cohort Study[78]	41 mother-infant dyads Sample consists of only black women	5	Physical abuse, Sexual abuse, Emotional abuse, Physical neglect, Emotional neglect *Measured: Childhood Trauma Questionnaire-Short Form* [75]	45	Cognitive development *(Brain Development-Frontoamygdala Connectivity)*	Maternal emotional neglect associated with amygdala- dorsal anterior cingulate cortex connectivity across both brain hemispheres (Left hemisphere: ΔR^2=0.2, 95%CI (0.01, 0.004), p=0.002. Right hemisphere: ΔR^2=0.9, 95%CI (0.001, 0.004), p=0.04), and with amygdala-ventromedial prefrontal cortex connectivity across the left hemisphere of the brain (ΔR^2=0.11,95%CI (0.002,0.03), p=0.03), which are both signs of impaired brain development No significant associations with physical, sexual, and emotional abuse, as well as physical neglect ACEs.	23
Hetherington et al[60]	Canada-urban setting	Data source: All our Families Cohort[79] Years: Women who were pregnant	1688 mother-infant dyads	10	Physical abuse, Sexual abuse, Emotional abuse, Physical neglect, Emotional neglect, Domestic Violence, Parental substance abuse, Parental separation/divorce, Parental mental health difficulties and Parental	62	Emotional Development *(Internalising behaviour and externalising behaviour)*	**Internalising behaviour:** Maternal ACE exposure not significantly associated with internalising behaviour (OR=1.19, 95%CI (0.82, 1.73)) **Externalising behaviour**: High exposure of mothers to ACEs significantly associated	22

		between 2008 and 2010			imprisonment *Measured: Original ACE Questionnaire*[73]			with child externalising behaviour (OR=1.98, 95%CI (1.26, 3.11))	
McDonald et al[61]	Canada-urban setting	Data source: All our Families Cohort[79] Years: Women who were pregnant between 2008 and 2011	1994 mother-infant dyads	7	Physical abuse, Sexual abuse, Emotional abuse, Domestic Violence, Parental substance abuse, Parental separation/divorce, Parental mental health difficulties *Measured: Original ACE Questionnaire* [73]	62.4	Emotional Development *(Internalising behaviour, Externalising behaviour, and child temperament)*	**Internalising behaviour:** Children of mothers who experienced high levels of ACEs statistically more likely to display internalising behaviours (emotion disorder (OR= 1.46 95%CI (1.06–2.02)), separation anxiety (OR=1.32 95%CI (1.03–1.70))) **Externalising behaviour:** Children of mothers who experienced high levels of ACEs statistically more likely to display externalising behaviours (inattention: OR-1.5, 95%CI (1.16, 1.94)), physical aggression (OR=1.61, 95%CI (1.21, 2.13))) **Child temperament:** Children of mothers who experienced high levels of ACEs statistically more likely to display sub-optimal domains of child temperament (surgency (OR=1.31, 95%CI (1.01, 1.69)), negative affectivity (OR=1.68, 95%CI (1.31-2.17)))	24
Moog et al[49]	USA-clinical convenience setting	Primary data collected specifically for study	80 mother-infant dyads	5	Physical abuse, Sexual abuse, Emotional abuse, Physical neglect, Emotional neglect *Measured: Childhood Trauma Questionnaire*[75]	35	Cognitive development *(Brain development- brain tissue volumes)*	Newborns of mothers with a history of child maltreatment had a significantly smaller intracranial volume (F1,70 = 6.84, p = .011, padj = .022, partial η2 = .089), but not with hippocampus or amygdala volume. Newborns of mothers with a history of child maltreatment had a significantly smaller overall brain size	22
Myhre et al[62]	Norway-population based sample	Data Source: Norwegian Mother and Child Cohort Study[80]	25,452 mother-infant dyads	3	Physical abuse, Sexual abuse, and Emotional abuse *Measured: Norvold Abuse Questionnaire* [81]	17.5	Emotional Development *(Externalising behaviour)*	Maternal childhood abuse exposure significantly associated with offspring externalising behaviours at three years of age (p<0.001)	23

Noll et al[50]	USA-urban setting	Primary data collected specifically for study	71 mother-infant dyads	1	Sexual abuse *Measured: referment by child protective services*	56.3	Childhood growth *(Preterm birth)*	Maternal childhood sexual abuse experience was a significant predictor of preterm delivery status (OR: 2.8±1.44, 95%CI= ±0.37, p<0.05).	22
Pear et al[51]	USA-population based setting	Data Sources: US national longitudinal survey of youth[82]. NLSY79 Children and Young Adults Survey[83] Year: 1979 and 1986	2999 mothers and 6596 children	3	Physical abuse, Parental substance abuse and Parental mental health difficulties *Measured: Original ACE Questionnaire*[73]	36	Risk-taking behaviours *(Smoking)*	Maternal childhood exposure to physical abuse and parental substance abuse was significantly associated with a 20% and 17% increased risk of offspring smoking, retrospectively. Maternal childhood exposure to parental mental health not a risk factor	23
Plant et al[58]	UK-population based setting	Data Source: Avon Longitudinal Study of Parents and Children (ALSPAC)[76] Years: 1991-1994	9397 mother-infant dyads	5	Physical abuse, Sexual abuse, Emotional abuse, Physical neglect, Emotional neglect *Measured: maternal self-report questionnaire (unvalidated measure)*	27	Emotional Development *(Internalising behaviour and externalising behaviour)*	**Internalising behaviour:** maternal childhood maltreatment exposure significantly associated with offspring internalising behaviour **Externalising behaviour:** maternal childhood maltreatment exposure significantly associated with offspring externalising behaviour	23
Roberts et al[53]	USA-population based setting	Data Source: Nurses' Health Study II[84] Year: 2001	54,963 mother-infant dyads Cohort study of female nurses	3	Physical abuse, Sexual abuse, and Emotional abuse *Measure: Childhood Trauma Questionnaire*[75]	NA (estimated sexual abuse= 36, physical/ emotional abuse =66.6)	Physical/mental health conditions/ disorders *(Autism)*	Women exposed to the most severe forms of childhood physical or emotional abuse significantly more likely to have a child with autism (p=0.003). Childhood sexual abuse, or low severity levels of physical or emotional abuse exposure, not statistically significant. • children of mothers exposed to childhood physical, sexual and emotional abuse were significantly more likely to be both overweight (RR	21

								= 1.14 – 1.21, 95%CI (1,02, 1.33), p<0.0001) and obese (RR = 1.23-1.45, 95%CI (1.21, 1.74), p<0.01) • Women who had been exposed to the highest level of childhood abuse were at a 61.1% elevated risk of having an autistic child.	
Roberts et al[52]	USA-population based setting	Data Source: Nurses' Health Study II[84] Year: 2001	16882 mother-infant dyads Cohort study of female nurses	3	Physical abuse, Sexual abuse, and Emotional abuse *Measured: Childhood Trauma Questionnaire (Physical and Emotional abuse subscale)* [75]	59.7	Physical/mental health conditions/ disorders and Risk-taking behaviours *(Offspring BMI and smoking)*	**Physical and mental health:** • Maternal childhood abuse associated with a higher offspring BMI: overweight (RR= 1.14-1.21, 95%CI (1.02,1.33)), obesity (RR=1.23-1.45, 95%CI (1.21, 1.74)) • children of mothers exposed to childhood physical, sexual and emotional abuse were significantly more likely to be diagnosed as autistic by age 3 (RR= 3.7, 95%CI (2.3, 5.8), p<0.001) **Risk-taking behaviour (smoking):** • Maternal childhood abuse associated with offspring following highest risk smoking trajectory (RR=1.41, 95%CI (1.21, 1.64)) • mothers' exposure to childhood abuse was a significant predictor of her offspring smoking (OR= 1.16-1.4, 95%CI (1.02, 1.61), p<0.001).	22
Shih et al[54]	USA-urban setting	Data source: Urban Child Institute CANDLE study[70]	1030 mother-infant dyads	3	Physical abuse, Sexual abuse and domestic violence *Measured: Traumatic Life Events Questionnaire*[71]	36	Emotional development (*Internalising behaviour)*	Small but significant association between maternal ACEs and child internalising behaviours at the age of 4-6 (beta=0.1, p<0.01)	21

		Year: 2006-2011							
Zvara and Burchinal[5] [5]	USA-rural poverty setting	Data Source: Family Life Project	348 mother-infant dyads Low-income, African American families	1	Sexual abuse *Measured: Trauma history Questionnaire*[85]	46	Emotional Development and Educational attainment *(Socioemotional development and educational attainment at kindergarten and first grade)*	**Emotional Development:** Maternal childhood sexual abuse exposure significantly associated with greater oppositional behaviour (beta=0.33, p<0.05), peer problems (beta=0.14, p<0.05) and conduct problems (beta=0.28, p<0.01) in offspring. **Educational attainment:** Maternal childhood sexual abuse exposure significantly associated with reduced expressive language skills (beta=0.49, p<0.05). No significant associations with reading or maths skills.	22

*Where data was collected from a pre-existing cohort, the name and year cohort data was collected is identified. When primary data was collected specifically for study, this is noted

Appendix 3: PRISMA 2020 checklist

The PRISMA checklist completed for this review to guide the main body text. (Page *et al.*, 2021 (A); Page *et al.*, 2021 (B)).

Section and Topic	Item #	Checklist item	Page where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5

Section and Topic	Item #	Checklist item	Page where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	17	Cite each included study and present its characteristics.	8-16
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9-15
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-15
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	16-18
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	16-18
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	16-18
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	18-19
	23b	Discuss any limitations of the evidence included in the review.	19
	23c	Discuss any limitations of the review processes used.	19
	23d	Discuss implications of the results for practice, policy, and future research.	20
OTHER INFORMATION			

Section and Topic	Item #	Checklist item	Page where item is reported
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix 4: PRISMA 2020 checklist for abstracts

The PRISMA checklist completed for this review to guide the abstract text. Page *et al.*, 2021 (A); Page *et al.*, 2021 (B)).

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	No
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesise results.	No
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	NA
Registration	12	Provide the register name and registration number.	Yes

Appendix 5: CASP critical appraisal of studies included in this review

A breakdown of the overall critical appraisal score from the CASP tool (Critical Appraisal Skills Programme, 2018). A score of 2 indicates that the criterion was completely met, a score of 1 indicates criterion was partially met, and a score of 0 indicates criterion not met or mentioned. The maximum score a study could obtain was 24. Following Njau et al[37] guidance on scoring, a study total score of ≥20 indicates that the study was judged as high quality, 16-19 indicates that the study is of moderate quality, and a score of ≤15 indicates study is of low quality.

	McDonald *et al.*, 2019	Myhre *et al.*, 2014	Zvara and Burchinal., 2019	Noll *et al.*, 2007	Folger *et al.*, 2018	Pear *et al.*, 2016	Esteves *et al.*, 2020	Hethering ton *et al,*, 2020	Hendrix *et al.*, 2021	Eismann *et al.*, 2019	Adgent *et al.*, 2019	Roberts *et al.*, 2014	Collisha w *et al.*, 2007	Fenerci and Allen., 2018	Choi *et al.*, 2019	Plant *et al.*, 2017	Roberts *et al.*, 2013	Moog *et al.*, 2018	Shih *et al.*, 2020	Ciciolla *et al.*, 2021	Beveridge *et al.*, 2022
Did the study address a clearly focused issue?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Was the cohort recruited in an acceptable way	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	2	2
Was the exposure accurately measured to minimise bias?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Was the outcome accuratley measured to minimise bias?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Have the authors identified all important confounding factors?	2	2	2	2	2	2	2	2	2	1	0	2	2	1	2	2	2	2	1	2	1
Have they taken account of the confounding factors in the design and/or analysis?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1
Was the follow up of subjects complete enough?	2	1	1	1	1	1	1	2	2	1	2	1	1	1	1	1	1	2	1	1	2
Was the follow up of subjects long enough?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Are the results precise?	2	2	2	2	1	2	2	1	2	2	2	2	2	2	2	2	1	2	2	1	2
Do you believe the results?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1
Can the results be applied to the local population?	2	2	1	1	1	2	2	1	1	1	1	1	2	1	1	2	2	1	2	1	0
Do the results of this study fit with other available evidence?	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	1	2	2
Total=	**24**	**23**	**22**	**22**	**21**	**23**	**23**	**22**	**23**	**21**	**20**	**22**	**23**	**20**	**22**	**23**	**21**	**22**	**21**	**21**	**19**