BMJ Open

Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-063826
Article Type:	Original research
Date Submitted by the Author:	14-Apr-2022
Complete List of Authors:	Mamun, Abdullah; Queensland University of Technology Biswas, Tuhin; University of Queensland, Scott, James; University of Queensland Sly, P.D.; University of Queensland, Queensland Childrens Medical Research Instit McIntyre, David; Mater Research Institute The University of Queensland Thorpe , Karen ; University of Queensland Boyle , Frances; University of Queensland Dekker, N; University of Queensland, Centre for Clinical Research Doi, Suhail; Qatar University, Population Medicine Mitchell, Murray; QUT, Faculty of Health, School of Biomedical Sciences McNeil, Keith; Queensland Health Kothari, Alka ; University of Queensland Hardiman, Leah; Queensland Health Callaway, Leonie Kaye; Queensland Health
Keywords:	Epidemiology < TROPICAL MEDICINE, EPIDEMIOLOGY, Adverse events < THERAPEUTICS, Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, Prenatal diagnosis < OBSTETRICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Author's names: Abdullah Al Mamun, PhD[1,2]; Tuhin Biswas, PhD[1,2]; James G. Scott, PhD[3,4,5]; Peter D Sly, MD; DSc[6]; David McIntyre, PhD[7]; Karen Thorpe, PhD[1,2]; Fran Boyle, PhD[1]; Marloes Dekker Nitert, PhD[8]; Suhail A. R. Doi, PhD[9,10]; Murray Mitchell, PhD[11]; Keith McNeil, PhD[12]; Alka Kothari, MD FRANZCOG[13,14]; Leah Hardiman MSC[15]; Leonie Callaway, PhD[15]

Author affiliations:

1. Institute for Social Science Research, The University of Queensland, QLD, Australia
2. ARC Centre of Excellence for Children and Families over the Life Course, The University of Queensland, QLD, Australia
3. Mental Health Research Program, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia
4. Metro North Mental Health, Royal Brisbane and Women's Hospital, Herston, QLD, Australia
5. Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, QLD, Australia
6. Children's Health and Environment Program, Child Health Research Centre, The University of Queensland, QLD, Australia
7. Mater Research, Faculty of Medicine, University of Queensland, Mater Health, QLD, Australia.
8. School of Chemistry and Molecular Biosciences, The University of Queensland, QLD, Australia
9. Research School of Population Health, Australian National University, Canberra, Australian Capital Territory
10. Department of Population Medicine, College of Medicine, Qatar University, Doha
11. Faculty of Health, School of Biomedical Sciences, The Queensland University of Technology, QLD, Australia
12. Prevention Division, Queensland Health, QLD, Australia
13. Department of Obstetrics & Gynaecology, Redcliffe Hospital, Anzac Avenue, Redcliffe, QLD, Australia
14. Faculty of Medicine, The University of Queensland, QLD, Australia
15. Women's and Children's Stream - Metro North Hospital and Health Services, QLD, Australia

Corresponding author:
Abdullah Al Mamun
Institute for Social Science Research,
The University of Queensland
80 Meiers Road, Indooroopilly, Queensland 4068, Australia.
Email: mamun@sph.uq.edu.au
Telephone: +61 7 336 53163

ABSTRACT

Objective To summarise the available clinical evidence on the association between ACEs and risk of pregnancy complications and adverse pregnancy outcomes.

Design Overview of systematic review and meta-analysis. CRD42021278030

Data sources A comprehensive search on PubMed, EMBASE, CINAHL, PsycINFO and Google scholar on all relevant studies published on the association between ACEs and risk of pregnancy complications and adverse birth outcomes up to July 2021 was performed.

Eligibility criteria for selecting studies Population was pregnant women, reported any ACEs including childhood maltreatment, childhood trauma or childhood hardship/suffering and if studies reported any pregnancy-related complications

Data extraction and synthesis Two independent reviewers (TB and AAM) carried out the data extraction. Meta-analysis using the quality-effects model on the reported odds ratio (OR) was conducted. Heterogeneity and inconsistency were examined using the Q and I^2 statistics.

Results Thirty-two studies from 1,303 met *a priori* inclusion criteria for systematic review, with 20 included in the meta-analysis. Pooled analyses showed that exposure to ACEs increased the risk of pregnancy complications (odds ratio, OR=1·3, 95% CI: 1·14-1.4) and adverse pregnancy outcomes (OR=1·23, 95% CI: 1·17-1·3). In sub-group analysis, maternal ACEs were associated with gestational diabetes mellitus (OR=1·2, 95% CI: 0·9-1·5), antenatal depression (OR=1·5, 95% CI: 1·2-2·2), low offspring birth weight (OR=1·2, 95% CI: 1·2-1·3), and preterm delivery (OR=1·2, 95% CI: 1·2-1·3).

Conclusion The results suggest that exposure to ACEs increase the risk of pregnancy complications and adverse pregnancy outcomes. Preventive strategies, screening and trauma informed care need to be examined to improve maternal and offspring health.

Key questions

What is already known?

- Pregnant women exposed to ACEs are considered a vulnerable group because adverse events in early life are associated with an increased risk of complications during pregnancy and adverse birth outcomes.
- Several systematic reviews, with or without meta-analysis, have reported associations between ACEs and preterm birth, low birth weight, and depression/anxiety during pregnancy.
- None have investigated the association of ACEs and the risk of pregnancy complications including gestational diabetes, hypertensive disorder in pregnancy, excess gestational weight gain, depression/anxiety during pregnancy and adverse pregnancy outcomes such as preterm birth and preterm birth and low birth weight.

What are the new findings?

- Maternal ACEs were associated with an increased risk of pregnancy complications, including GDM, GWG, HDP and depression/anxiety during pregnancy.
- ACE exposure showed a significant association with any adverse pregnancy outcome.
- For each additional unit increase in the number of ACEs, the odds of adverse pregnancy outcomes increased 1.10 times.

What do the new findings imply?

- Preventive strategies, screening and trauma informed care need to be examined to improve maternal and offspring health.
- It may be valuable to assess the role of routine ACE screening during pregnancy to improve maternal and child health.

INTRODUCTION

Adverse Childhood Experiences (ACEs)[1] are psychosocial stressors and traumas experienced by an individual before 18 years of age[2,3] The pioneering study by Fellitti and colleagues (1998) demonstrated that exposure to ACEs is common, ACEs co-occur and that exposure to multiple ACEs are associated with an increased risk of health risk behaviours and illnesses.[4] Subsequently, a growing body of research has continued to provide consistent evidence that ACEs are a major public health issue due to their high prevalence and harmful effects that ACEs have on human health throughout life.[5,6]

Early life experiences are recognized as essential determinants for health outcomes later in life especially in pregnant women and their children[7]. Adverse health outcomes in pregnancy can then result in intergenerational transmission of adverse health outcomes. Perhaps this occurs because women who have experienced ACEs may be a vulnerable group for development of health risk behaviours, including smoking, drug and alcohol use and sedentary lifestyle, along with consequences of trauma such as poor sleep.[5] These behaviours increase the risk of pregnancy complications including gestational diabetes mellitus (GDM), hypertensive disorder of pregnancy (HDP), excess gestational weight gain (GWG), depression/anxiety during pregnancy [8] and adverse pregnancy outcomes including low birth weight and preterm birth.[9-11] Systematic reviews have reported women who had experienced child maltreatment are more likely to have pregnancy complications and that physical abuse and household substance abuse were associated with greater risk of GDM[12,13] resulting in intergenerational transmission of adverse health outcomes. Overall, those reporting exposure to multiple ACEs (mostly 4 or more) have an increased risk of physical, mental, and substance use disorders.[14]

Evidence on ACEs and the associated risk of pregnancy complications and adverse birth outcomes is inconclusive. A longitudinal study in Australia reported that women exposed to three or more ACEs had an elevated GDM risk.[15] In contrast, a longitudinal study from the USA reported no significant association between ACEs (for each score change and reported 4 or more ACEs) and GDM.[16] A systematic review suggests that total ACEs (score in continuous scale) are associated with preterm birth, although this finding needs to be confirmed in other studies to explore the associations between ACEs and preterm birth using appropriate and valid instruments.[17] Another systematic review and meta-analysis reported that maternal history of abuse before pregnancy was significantly associated with preterm delivery and low

birth weight.[18] No systematic review and meta-analysis has investigated the association of ACEs and the risk of pregnancy complications including GDM, HDP, GWG, depression/anxiety during pregnancy and adverse pregnancy outcomes. This study aims to systematically review and meta-analyse existing studies to establish the extent of association between ACEs and pregnancy complications and adverse birth outcomes. Understanding these associations will inform maternal clinical care and support for offspring of those women exposed to ACEs.

METHODS

In this systematic review and meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [19] and the Meta-Analysis of Observational Studies in Epidemiology protocol [20] to ensure all necessary steps were followed. In accordance with the guidelines, the systematic review and meta-analysis protocol was registered in PROSPERO (CRD42021278030).

Literature search strategy

Our search included studies published to July 10, 2021 using PubMed, EMBASE, CINAHL, and PsycINFO. The search strategy employed with PubMed is: ((((((((((("adverse childhood experiences") OR ("childhood adversities")) OR ("childhood abuse")) OR ("childhood maltreatment")) OR ("child trauma")) OR ("adverse childhood events")) OR ("childhood sexual abuse")) OR ("childhood physical abuse")) OR ("childhood mental abuse")) OR ("childhood trauma")) OR ("childhood violence")) OR ("childhood hardship")) OR ("childhood suffering")) OR ("childhood Stress")) AND ((((((((((("pregnancy complications") OR ("Depression")) OR ("Anxiety")) OR ("Prenatal depression")) OR ("Depressive symptoms")) OR ("Antenatal depression")) OR ("Mental health problem")) OR ("gestational diabetes mellitus")) OR ("GDM")) OR ("hypertensive disorder of pregnancy")) OR ("HDP")) OR ("preeclampsia")) OR ("maternal body weight")) OR ("excess weight gain")) OR ("abnormal fetal growth")) OR ("Intrauterine growth restriction")) OR (Low birth weight)) OR (LBW)) OR (IUGR)) OR (Stillbirth)) OR (small of gestational age)) OR ("preterm birth")).

Inclusion criteria

Studies were included if the full-text was published in English, population was pregnant women, reported any ACEs including childhood maltreatment (childhood physical, emotional and sexual abuse, childhood physical and emotional neglect and exposure to parental intimate partner violence), childhood trauma or childhood hardship/suffering and if studies reported any pregnancy-related complications according to National Institute of Health (NIH)[21] (GDM, HDP, GWG, depression/anxiety during pregnancy) and adverse birth outcomes such as low birth weight, intra-uterine growth restriction (IUGR), preterm birth, stillbirth. Studies were excluded if: (1) published in languages other than English; (2) included general population (not pregnant); (3) reported reviews, qualitative studies, editorials, abstracts, case reports and letters to the editor or (4) explored violence during pregnancy.

Data extraction

Two independent reviewers (TB and AAM) carried out the data extraction. If AAM and TB did not reach agreement, the small group (AAM, TB, LC and JS) discussed discrepancies to reach a consensus. A similar approach was used for full text reviews. Relevant data from each of the selected studies was extracted including first author; study title; country of study; sample size; study design; types of ACEs; measurement scale; and outcomes (both risk of pregnancy complications and adverse pregnancy outcomes) and recorded on an Excel spreadsheet.

Quality assessment

Fifteen-point scale quality assessment tools were used to assess the quality and risk of bias of the studies. We adapted a quality assessment tool from NIH "Quality Assessment Tool for Observational Cohort and Cross-sectional studies".[22] This tool allowed assessment of the question, population, participation, inclusion/exclusion criteria, sample size, exposures, timeframe, levels of exposure, independent variables, longitudinal/repeated ACEs, dependent variable, objectively measured independent variables, objectively measured dependent variables, lost to follow-up and confounders (**Supplementary Table 1)**. The results of the quality assessment are presented in **Supplementary Table 2.**

Data Analysis

Analyses focused on the overall association between ACEs and risk of pregnancy complications and adverse birth outcomes. Subgroup data synthesis was performed only when three or more studies were available with the estimates for a similar type of ACE exposures. ACE scores were considered on the continuous scale (for each unit change) and three categories: i) none versus at least one ACEs; ii) one to three as low ACEs; and (iii) four or more as high ACEs. Although most of the studies reported the odds ratio (OR) as the measurement of association between exposures and outcomes, two studies reported relative risk (RR) and one hazard ratio (HR). We converted all measures of associations into ORs using conversion methods reported elsewhere. [23] In the meta-analysis, we used the quality effects model (QE) [24] for bias adjustment. The advantage of the QE model is that the between-study variability is adjusted based on the relative quality rank of the studies instead of on random variables assigned by the random effect (RE) model. The heterogeneity of the studies was reported by the I-squared value (I^2) that measures the proportion of total variance between studies beyond random error.[24] We checked for publication bias through visualization by funnel plot and Doi plot.[25] All the analyses were conducted using the MetaXL software version 5.3.[26]

Patient and Public Involvement

No patient involved

RESULTS

The literature search resulted in 1,303 records, which were screened for duplication (n=227), review of titles (n=1,076) and further abstract evaluation (n=475). Finally, 32 studies met our inclusion criteria for full text review, and 20 were included in meta-analysis **(Figure 1)**. 75% of the studies (n =24) were cohort studies and the remainder were either cross sectional or case-control studies. The majority of the studies were conducted in the USA (n = 20), with fewer studies from Canada (n=3), Europe (n=5) and other regions (n=4). The study sample sizes varied from 48 to 11,556. The publication year ranged from 1994 to 2021. Thirteen studies used the 10-item ACEs questionnaire8,16,27-37, three used World Health Organization (WHO) ACE-IQ questionnaires38-40 with one study used 8-items 41 and other study sued 19-items questionnaire42 and fourteen studies used other measures 35,43-53 **(Table-1 and 2)**.

Table 1: Characteristics of Studies included in the systematic review and meta-analysis

SI#	First Author/Pub Date	Country	Study design	Sample size	Type of Abuse	Measurement scale	Outcomes
1	Christiaens/2015	Canada	Case-control	622	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	Preterm birth
2	Grimstad/ 1999	Norway	Case-control	174	Sexual Abuse	Were asked about the character of the experience(s): • Genital Touch • Forced to touch the other person's genitals • Attempted Coitus; 4. Penile Vaginal Coitus	• Preterm birth • Low birth weight (<2500g)
3	Noll/ 2007	USA	Cohort	186	Sexual abuse	• Childhood sexual abuse	• Preterm birth
4	Leeners/ 2014	Switzerland	Cohort	255	Sexual abuse	• Childhood sexual abuse experiences were additionally explored using questions modified from a questionnaire developed by Wyatt	• Preterm birth
5	Selk/2016	USA	Case-control	51434	Physical abuse Sexual abuse	• The measure of physical abuse included items from the Revised Conflict Tactics Scale (CTS) • The sexual abuse measure was derived from the survey by Finkelhor et al	Preterm birth
6	Harville/2010	UK	Cohort	4865	Violence	The phrase "childhood hardship" is used herein to refer to a num-ber of adverse situations in childhood: • Financial/structural hardship • No interest in education • Family dysfunction • Lack of supportive caregiving • Violence/mental health issues • Issues of family structure • No. of hardships	• Preterm birth • Low birth weight(<2500g)
7	Appleton et al, 2019	USA	Cohort study	126	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	Depressive symptoms during pregnancy
8	Versteegen et al., 2021	USA	Cohort	300	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	GDM
9	Stanhope et al., 2020	USA	Cohort	2319	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	GDM HDP
10	Schoenaker et al., 2019	Australia	Cohort	11,556	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	GDM
11	Miller et al., 2017	USA	Prospective study	744	Childhood economic hardship	asked women a series of questions about their family's conditions during childhood	birth outcomes
12	Mersky et al., 2019	USA	Longitudinal	1848	ACEs	19-item assessment that has demonstrated good internal consistency	Pregnancy loss (< 20 weeks gestation) preterm birth low birthweight (<2500 g)
13	Mason et al., 2016	USA	Cohort	45,550	Physical abuse	• Physical abuse • Sexual abuse	GDM

14	Cammack et al., 2018	USA	Cohort	230	Physical abuse	Childhood Trauma Questionnaire Short-Form (CTQ)	• Low Birth Weight (<2500g) • Preterm Birth
15	BALA et al., 2020	Rhode Island	Population-based survey	3350	ACEs	7-item questionnaire	GDM
16	Ben Salah et al, 2019	Tunisia	Prospective follow-up study	593	ACEs	ACE-International Questionnaire (ACE-IQ)	• Preterm Birth • Low birth weight
17	Bhengu, 2019	South Africa	cross-sectional	223	ACEs	WHO-ACE IQ	• Preterm Birth
18	Gillespie et al. (2017)	USA	Prospective observational design	89	Childhood stress	The Stress and Adversity Inventory (STRAIN)	Birth timing
19	Leeners et al, 2014	Switzerland	cohort	225	CSA, physical abuse experiences, and other ACE	using questions modified from a questionnaire developed by Wyatt	Preterm Birth
20	McDonnell et al, 2014	USA	Cohort	398	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	GDM
21	Shaikh et al., 2019	Pakistan	Cohort	300	ACEs	World Health Organization 31-item ACEs –International Questionnaire (ACE-I	Preterm Birth
22	Smith et al., 2016	USA	Cohort	2303	ACEs	The main modification of the instrument was to collapse the sexual events before the age of 18 questions into 1 question asking about childhood sexual abuse prior to age 18.	• Birth weight • Shorter gestational age
23	Ranchod et al, 2016	USA	Longitudinal study	2,873	• Physical abuse • Household alcohol abuse • Household mental illness	4-Item questionnaire	GWG
24	Fredriksen et al, 2017	Norway	Cohort	762	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	• Depression • Anxiety
25	Hantsoo et al,2019	USA	Observational study	48	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	Depression
26	Howell1,2019	USA	Observational study	101	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	Depression
27	Letourneau et al, 2019	Canada	Cohort	907	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	Depression
28	Narayan et al, 2018	USA	Cohort	101	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	Depression
29	Racine et al, 2020	Canada	Cohort	1994	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	Depression
30	Young-Wolff et al, 2019	USA	Cohort	355	ACEs	10-item self-report tool developed after the original ACE study by Felliti et al	Depression
31	Barrios et al, 2015	USA	Cohort	1,521	Childhood physical and sexual abuse	Eight questions concerning abuse taken from the Centers for Disease Control and Prevention (CDC) Adverse Childhood Experiences Study	Depression

Table 2: Summary of published measures of effect.

SI#	First Author/Pub Date	Outcomes	Types of ACEs and analytical unit	Findings (OR, 95% CI)
1	Christiaens et al·, 2015	Preterm birth	High ACE score (≥2 ACE)	2·09, (1·10–3·98)
			ACE's score (continuous)	1·18, (0·99–1·40)
2	Grimstad et al·,1999	Preterm birth	Sexual Abuse	1·03, (0·44-2·4)
		Low birth weight	Sexual Abuse	1·21, (0·5-2·93)
3	Noll et al·, 2007	Preterm birth	Sexual abuse	2·16, (0·77-6·06)
4	Leeners et al·, 2014	Preterm birth	Sexual abuse	2·47, (1·11-5·51)
5	Selk et al·, 2016	Preterm birth	Severe physical only	1·02, (0·88- ·17)
			Forced sex only	1·22, (1·1-1·35)
			Experienced both severe abuse types	1·35, (1·13-1·62)
6	Harville et al·, 2010	Preterm birth	Financial/structural hardship	1·20 (0·90-1·60)
			No interest in education	1·17 (0·93-1·48)
			Family dysfunction	1·20 (0·94-1·52)
			Lack of supportive caregiving	0·98 (0·81-1·19)
			Violence/mental health issues	1·24 (0·94-1·63)
			Issues of family structure	1·25 (1·02-1·54)
			No· of hardships (≥ 4)	1·45 (1·09-1·93)
		Low birth weight	Financial/structural hardship	1·18 (0·88-1·60)
			No interest in education:	1·18 (0·88-1·60)
			Family dysfunction	1·18 (0·88-1·60)
			Lack of supportive caregiving	1·18 (0·88-1·60)
			Violence/mental health issues	1·48 (1·12-1·96)
			Issues of family structure	1·48 (1·12-1·96)
			No· of hardships (≥ 4)	1·48 (1·12-1·96)
7	Appleton et al, 2019	Depression	ACE's score (continuous)	Pearson's correlations coefficients (0·37)
8	Versteegen et al·, 2021	GDM	ACEs total	1·00 (0·84, 1·18)
			ACEs binary	1·31 (0·50, 3·39)
9	Stanhope et al·, 2020	GDM	ACEs 4+	1·03 (0·71, 1·49)
			Continuous ACE score	0·96 (0·88, 1·04)
		HDP	ACEs 4+	1·03 (0·71, 1·49)
			Continuous ACE score:	1·03 (0·71, 1·49)
10	Schoenaker et al·, 2019	GDM	Three ACEs	1·73, (1·02, 3·01)
			Four or more ACEs	1·76, (1·04, 2·99)
11	Miller et al·, 2017	Birth outcomes	Childhood economic hardship	Mother's hardship independently associated with multiple adverse birth outcomes
12	Mersky et al·, 2019	Preterm birth	ACE scores (continuous)	1·07, (1·01–1·12)
			1 or 2 ACEs	1·22 (0·79–1·89)
			3 or 4 ACEs	1·29 (0·82–2·02)
			5 or more ACEs	1·46 (0·95–2·26)
		Low birthweight	ACE scores (continuous)	1·08, (1·03–1·15)
			1 or 2 ACEs	0·98 (0·62–1·56)
			3 or 4 ACEs	1·22 (0·76–1·96)
			5 or more ACEs	1·39 (0·88–2·19)
		Pregnancy loss	ACE scores (continuous)	1·12, (1·08–1·17)
			1 or 2 ACEs	0·93 (0·66–1·31)
			3 or 4 ACEs	1·27 (0·89–1·80)

			5 or more ACEs	1·27 (0·89–1·80)
13	Mason et al·, 2016	GDM	Mild physical abuse	1·08 (0·96, 1·22)
			Moderate physical abuse	11·16 (1·04, 1·29)
			Severe physical abuse	1·42 (1·21, 1·66)·
			Forced sexual activity	1·30 (1·14, 1·49)
			Combine	1·42, (1·21, 1·66)
14	Cammack et al·, 2018	Low Birth Weight	Emotional Abuse	0·88 (0·66–1·00) Cohen's Kappas (95% CI)
			Physical Abuse	0·50 (0·01–0·99)
			Sexual Abuse	0·75 (0·43–1·00)
			Emotional Neglect	0·59 (0·18–1·00)
			Physical Neglect	0·28 (−0·16–0·73)
		Preterm Birth	Emotional Abuse	0·78 (0·55–1·00)
			Physical Abuse	0·69 (0·36–1·00)
			Sexual Abuse	0·78 (0·55–1·00)
			Emotional Neglect	0·44 (0·12–0·77)
			Physical Neglect	0·39 (−0·03–0·81)
		NICU Admission	Emotional Abuse	0·58 (0·25–0·91)
			Physical Abuse	0·28 (−0·15–0·71)
			Sexual Abuse	0·73 (0·45–1·00)
			Emotional Neglect	0·55 (0·20–0·90)
			Physical Neglect	0·55 (0·20–0·90)
15	BALA et al·, 2020	GDM	3 or more ACEs	1·24, (0·81–1·90)
			1–2 ACEs	1·18, (0·90– 1·55)
16	Ben Salah et al, 2019	Preterm Birth Low birth weight	ACEs continuous	After adjustment for high-risk pregnancies, environmental tobacco smoke, and intra-familial ACEs, the risk of premature birth was significantly associated with exposure to collective violence (P < 0·001) and witnessing community violence (P < 0·05)·
17	Bhengu et al·, 2019	Preterm Birth	ACEs continuous	1·21, (1·03-1·43)
18	Gillespie et al· (2017)	Birth timing	ACEs continuous	Cumulative childhood stress predicted birth timing (p = 0·01)·
19	Leeners et al, 2014	Preterm Birth		CSA, physical abuse as well as other ACE were associated with an increased risk for premature delivery
20	McDonnell et al, 2014	GDM		GDM not correlated with ACE indicators
21	Shaikh et al·, 2019	Preterm Birth	ACEs continuous	We found no association between ACE and preterm birth
22	Smith et al·, 2016	Birth weight and shorter gestational age	ACEs continuous	Each additional ACE decreased birth weight by 16·33 g and decreased gestational age by 0·063·
23	Ranchod et al, 2016	GWG	Physical abuse	1·2, (1·1-1·4)
			Household alcohol abuse	1·2, (1·1-1·3)
			Household mental illness	1·1, (0·9-1·2)·
24	Fredriksen et al·, 2017	Depression	ACEs continuous	1·3, (0·92-1·82)
25	Hantsoo et al·,2019	Depression	< 2 ACES	EPDS (Median [IQR]): 5 [3, 6]
			2 or more ACES	EPDS (Median [IQR]): 3 [1·5, 6·0]
26	Howell et al·, 2020	Depression	ACEs continuous	Adverse childhood experiences had a direct effect on depression, B=1·11, standard error=·44, p=·01,
27	Letourneau et al, 2019	Depression	ACEs continuous	Maternal ACEs were associated with symptoms of anxiety and depression during pregnancy
28	Narayan et al et al·, 2018	Depression	ACEs continuous	Maternal ACEs were associated with depression during pregnancy (β = 0·32, p < 0·01)·
29	Racine et al et al·, 2020	Depression	ACEs continuous	1·26, (1·12-1·43)
30	Young-Wolff et al et al·, 2019	Depression	3+ ACEs	3·08, (1·12-7·39)
			1–2 ACEs	2·42 (1·09–5·41)
31	Barrios et al·, 2015	Depression		Depression: OR: 2·07; 95% CI: 1·58-2·71

ACEs and risk of pregnancy complications

ACEs and GDM: Six studies8,16,35,36,50,54 described an association between ACEs and GDM and only one study reported there was no association between ACEs and GDM [42]. A large epidemiological study in Australia 54 reported that, in pregnant women, exposure to any three ACEs (adjusted relative risk, aRR=1·7, 95% CI:1·0, 3·0) or four or more ACEs (aRR=1·7, 95% CI:1·0, 2·9) was associated with elevated GDM risk after adjusting preconception BMI, unhealthy diet, parity, and maternal age.. Another study in the USA by Mason et al., 201635 reported that both moderate (adjusted odds ratio, aOR=1·1, 95% CI:1·0, 1·2) and severe (aOR=1·42, 95% CI:1·2, 1·6) childhood physical abuse was associated with an increased risk of GDM. This study also reported that forced sexual activity during childhood was associated with an increased risk of GDM (aOR 1·3, 95% CI:1·1, 1·4).

ACEs, GWG and HDP

Only one study by Ranchod et al., 201653 examined the association between ACEs and GWG. They found that exposure to physical abuse and household alcohol abuse were independently associated with a 20% increase in the risk of excessive GWG. A study by Stanhope et al., 20208 found that for each ACEs score there was a slight increase in the HDP risk (aOR=1·0, 95% CI:0·9, 1·1), although it was not statistically significant. However, they found that physical abuse (aOR= 1·2, 95% CI: 1·1-1·4) and household alcohol abuse (aOR= 1·2, 95% CI: 1·1-1·3) were associated with a significant increase in the risk of excessive GWG.

ACEs and depression/anxiety

Nine studies27-33,37,41 examined the association between ACEs and depression/anxiety with almost all studies reporting a significant positive association during pregnancy. For example, a large cohort study in Canada by Racine et al, 202032 reported that ACEs were associated with depressive symptoms in pregnancy (aOR =1·2, 95% CI :1·1–1·4). Another study by Letourneau et al, 201930 reported that for each maternal ACE, there was an increased risk of symptoms of anxiety and depression during pregnancy. An observational study in the USA by Hantsoo et al28,29 reported that ACEs directly affected depression (B=1·1, standard error=·44, p=·01).

Meta-analytic results for maternal ACEs and risk of pregnancy complications

A total of 11 studies (72,889 participants) were available for the quality-effect meta-analysis, which produced an association between maternal any ACEs and risk of any adverse pregnancy complications (OR=1·3, 95% CI: 1·1-1·4) (Figure-2). In risk factor-specific sub-analysis, five studies (7116 participants) were available for meta-analysis, which produced a moderate association between maternal ACEs and risk of GDM (OR=1·2, 95% CI: 0·9-1·5). For depression/anxiety during pregnancy, four studies (6116 participants) were available for this meta-analysis, which produced an association between maternal ACEs and risk of depression/anxiety during pregnancy (OR=1·5, 95% CI: 1·15-2·2). Both low (OR=1·3, 95% CI: 1·1-1·5) and high (OR=1·4, 95% CI: 1·0-1·9) number of ACEs were associated with and any pregnancy complications (supplementary figure- 1.1). For every single unit increase of ACEs, the odds of pregnancy complications increased 1.12 times (OR=1·1, 95% CI: 0·9-1·3) (supplementary figure- 1.3).

ACEs and adverse pregnancy outcomes

ACEs and preterm birth: Out of 31 studies, 11 34,38,40,42-47,49,55 reported the association between ACEs and preterm birth. A study in Tunisia by Ben Salah et al. (2019) reported that after adjustment for high-risk pregnancies, environmental tobacco smoke, and intra-familial ACEs, the risk of premature birth was significantly associated with exposure to collective violence (P-value < 0.001) and witnessing community violence (P-value < 0·05). In another study, Harville et al47 reported that violence exposure during childhood was associated with a 44% increased risk of preterm birth (adjusted RR= 1·4; 95% CI: 1·0-1·9). They also found the family mental health issues increased by 24%, and a 25% increase in the risk of preterm birth. A case-control study in the USA by Selk et al46 reported that women exposed to forced sex during childhood had a 22% greater risk of preterm birth (adjusted RR=1·2, 95% CI: 1·1-1·3) than those in the no exposure group. Furthermore, exposure to physical and sexual abuse during childhood was associated with a 35% greater risk of preterm birth (adjusted RR=1·3, 95% CI: 1·1-1·6). A study by Miller et al., reported that mothers' childhood economic hardship was independently associated with multiple adverse birth outcomes.48 A study by Gillespie et al reported that maternal childhood abuse was associated with birth timing. 51

ACEs and low birth weight

Out of 31 studies, six 38,42,43,47,49,52 reported an association between ACEs and low birth weight. Harville et al reported that violence exposure during childhood was associated with an increased risk of low birth weight (adjusted OR= 1·5; 95% CI: 1·1-2·0). They also found that violence/mental health issues (adjusted OR=1·4, 95% CI:1·1-1·9) and issues of family structure increased the risk of low birth weight (adjusted OR=1·4, 95% CI:1·1-1·9). A study by Smith et al. reported that each additional ACE decreased gestational age at birth as well as birth weight. 52

Meta-analytic results for maternal ACEs and adverse pregnancy outcomes

A total of 12 studies were available for this quality-effects meta-analysis, which produced an association between maternal ACEs and any adverse pregnancy outcomes (OR=1·2, 95% CI: 1·1-1·3). In a sub-analysis of eight studies (59,607 participants), the quality-effects meta-analysis showed an association between maternal ACEs and preterm birth (OR=1·2, 95% CI: 1·1-1·2). On the other hand, three studies (7,014 participants) were available for the quality-effects meta-analysis for low birth weight, which showed an association between maternal ACEs and low birth weight (OR=1·2, 95% CI: 1·1-1·3) (Figure-3). In low (one to three ACEs) and high (four+) ACEs specific analysis, five studies reported low ACEs exposure and nine studies reported high ACEs exposure. Both low (OR=1·2, 95% CI: 1·0-1·5) and high (OR=1·3, 95% CI: 1·1-1·6) ACE exposure showed a significant association with any adverse pregnancy outcome (supplementary figure- 2). For each additional unit increase in the number of ACEs, the odds of adverse pregnancy outcomes increased 1.10 times (OR=1·1, 95% CI: 1·0-1·1) (supplementary Figure 2.3).

DISCUSSION

This systematic review and meta-analysis found that maternal ACEs were associated with an increased risk of pregnancy complications, including GDM, GWG, HDP and depression/anxiety during pregnancy. To our knowledge, this is the first systematic review, and meta-analysis to assess the association between ACEs and pregnancy complications. One previous systematic review and meta-analysis reported an association between ACEs and maternal mental health problems. [22] There could be many potential mechanisms to explain the relationship between ACEs and adverse pregnancy outcomes. Results from animal models [56,57] and longitudinal human studies such as the Nurses' Health Study have proposed that a strong history of ACEs may alter hypothalamic-pituitary-adrenal axis as reflected by elevated cortisol levels that in turn alter glucose metabolism and body weight regulation.[35] Brain development begins in fetal life and continues into early adulthood. Early life maternal ACEs alter the structure and function of the brain.[58,59] These neurodevelopmental alterations may result in neuroendocrine disruption of cortisol regulation, linked to glucose metabolism. [60,61] The limbic system is connected to the autonomic nervous system reactivity generating a fight/flight response resulting in cortisol secretion with immune, endocrine, metabolic and cardiovascular consequences. ACEs may alter stress regulatory pathways, resulting in long-term altered responses to stress.[62] Exposure to ACEs are also associated with an increased risk of health risk behaviours including substance use, physical inactivity and unhealthy diet4. Previous research has shown that ACEs are associated with pre-pregnancy obesity.[63] Any of these mechanisms could explain the transgenerational nature of obesity and diabetes in families affected by maternal ACEs. Chronic inflammation, unhealthy behaviours, poor sleep and altered stress regulatory pathways are risk factors for adverse pregnancy complications, including GDM, HDP and depression/anxiety. [64,65]

We also found that maternal ACEs are positively associated with adverse pregnancy outcomes, including preterm birth and low birth weight. Our results are more comprehensive than previous systematic reviews [66 67 18] due to the availability of 12 recent primary studies. Previously published literature has suggested that the experience of ACEs increases the risk of physical or sexual abuse during pregnancy and is associated with placental damage, uterine contractions, premature rupture of membranes, and genitourinary infections which ultimately increase the risk of preterm birth and low birth weight.[68] Another possible explanation for the observed associations between ACEs and pregnancy outcomes is that a maternal history of abuse before pregnancy and maternal experience of abuse and other stressors during a lifetime contribute to an individual's allostatic load.[69,70] When the allostatic load exceeds a threshold level, vulnerability for disease is increased 4, which may include adverse pregnancy outcomes. [71]

According to our findings and other systematic review evidence, it may be valuable to assess the role of routine ACE screening during pregnancy to improve maternal and child health. Trauma informed care is not well incorporated into clinical practice guidelines. Much of the emphasis in maternity care is on individual behaviour change, including advice about diet, exercise, smoking cessation and uptake of clinical care. Approaches that do not incorporate the personal experiences of trauma by women attending antenatal services may inadvertently cause iatrogenic harm. For many years, there has been an interest in improving pregnancy outcomes by focusing on a limited set of physical parameters that can easily be measured such as gestational weight gain, without attention to the underlying mechanisms.[72,73] Overall, studies of diet and exercise in pregnancy to reduce GDM, HDP and other adverse pregnancy outcomes have been disappointing.[74] A recent scoping review by Mishra et al[75] found that ACEs screening does not excessively disrupt clinic workflow. Furthermore, they reported that ACEs

screening is both acceptable for the patient and feasible for the provider. However, to determine if screening for ACEs is worthwhile, studies would need to be undertaken to assess if trauma informed clinical care translates to improved clinical outcomes for mother and offspring. [76]

There are some limitations to the current study, which reduce the generalisability of the findings. Firstly, most of the included studies are from high-income western countries. Secondly, due to the lack of data, we could not conduct the ACEs item-specific analysis. Thirdly, the dose-response relationship in all studies could not be assessed as different studies use different screening tools and cut-off values. Only five studies exploring pregnancy complications and five studies investigating adverse pregnancy outcomes could be assessed for a dose response relationship. Lastly, as we considered various types of ACE exposures in a single review, we expected much heterogeneity in the study methodologies, populations, exposures, and outcome identification. To address these limitations, the Quality Effect model, which incorporates the heterogeneity of effects across the studies and reduces the risk-of-bias assessment was used in the meta-analysis. Nevertheless, our study has several strengths considering the comprehensive nature of the inclusion criteria, including relevant studies published up to July 2021. In addition, we assessed the methodological quality of studies using standard tools appropriate for observational cohort and cross-sectional studies.

CONCLUSION

In conclusion, this systematic review and meta-analysis found that exposure to ACEs increases the risk of pregnancy complications and adverse pregnancy outcomes. Identification of women exposed to ACEs and personalising their care may provide opportunities to improve maternal and offspring mental and physical health.

Acknowledgments

This research was partially supported by the Australian Research Council Centre of Excellence for Children and Families over the Life Course.

Contributors

AAM and TB contributed towards literature search, data analysis and interpretation, figures and tables, and writing of the manuscript. AAM, TB, LC, JS, PS contributed towards the drafting of the protocol, review of the study design, data collection and interpretation and provided a critical review of the manuscript. AAM and SD contributed towards data management and analysis plan and provided oversight and interpretation of the analyses. AAM, DM, KT, FB, MN, MM, KM, AK, LH contributed towards the study design and editing. AAM and LC contributed towards the design of the manuscript, development of the protocol, and critical evaluation and interpretation of the results and critical review of the manuscript.

Funding No funding

Disclaimer No disclaimer

Competing interests All authors declare no competing interests.

Patient consent for publication Not required.

Ethics approval and consent to participate Not applicable.

Data availability statement Data are available in a public and open access repository. All data analysed or produced in the study are included in the article or uploaded as supplemental files.

References

1· Atzl VM, Narayan AJ, Rivera LM, Lieberman AF· Adverse childhood experiences and prenatal mental health: Type of ACEs and age of maltreatment onset· *Journal of family psychology* 2019; **33**(3): 304·

2· Hughes K, Bellis MA, Hardcastle KA, et al· The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis· *The Lancet Public Health* 2017; **2**(8): e356-e66·

3· Wickramasinghe YM, Raman S, Garg P, Hurwitz R· Burden of adverse childhood experiences in children attending paediatric clinics in South Western Sydney, Australia: a retrospective audit· *BMJ paediatrics open* 2019; **3**(1)·

4· Felitti VJ, Anda RF, Nordenberg D, et al· Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study· *American journal of preventive medicine* 1998; **14**(4): 245-58·

5· Petruccelli K, Davis J, Berman T· Adverse childhood experiences and associated health outcomes: A systematic review and meta-analysis· *Child abuse & neglect* 2019; **97**: 104127·

6· Schroeder K, Schuler BR, Kobulsky JM, Sarwer DB· The association between adverse childhood experiences and childhood obesity: A systematic review· *Obesity Reviews* 2021; **22**(7): e13204·

7· Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C· Life course epidemiology· *Journal of epidemiology and community health* 2003; **57**(10): 778·

8· Stanhope KK, Cammack AL, Perreira KM, et al· Adverse childhood experiences and lifetime adverse maternal outcomes (gestational diabetes and hypertensive disorders of pregnancy) in the Hispanic Community Health Study/Study of Latinos· *Annals of Epidemiology* 2020; **50**: 1-6·

9· Schetter CD, Tanner L· Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice· *Current opinion in psychiatry* 2012; **25**(2): 141·

10· Olsen JM· Integrative review of pregnancy health risks and outcomes associated with adverse childhood experiences· *Journal of Obstetric, Gynecologic & Neonatal Nursing* 2018; **47**(6): 783-94·

11· Dachew BA, Mamun A, Maravilla JC, Alati R· Association between hypertensive disorders of pregnancy and the development of offspring mental and behavioural problems: a systematic review and meta-analysis· *Psychiatry research* 2018; **260**: 458-67·

12· Montgomery E, Pope C, Rogers J· A feminist narrative study of the maternity care experiences of women who were sexually abused in childhood· *Midwifery* 2015; **31**(1): 54-60·

13· Montgomery E, Pope C, Rogers J· The re-enactment of childhood sexual abuse in maternity care: a qualitative study· *BMC pregnancy and childbirth* 2015; **15**(1): 1-7·

14· Lê-Scherban F, Wang X, Boyle-Steed KH, Pachter LM· Intergenerational associations of parent adverse childhood experiences and child health outcomes· *Pediatrics* 2018; **141**(6)·

15· Schoenaker DA, Callaway LK, Mishra GD· The role of childhood adversity in the development of gestational diabetes· *American journal of preventive medicine* 2019; **57**(3): 302-10·

16· Versteegen M, Bozlak CT, Larkin H, Appleton AA· Maternal depression, adverse childhood experiences, and social support in relation to gestational diabetes risk: results from the Albany Infant and Mother Study (AIMS)· *BMC Pregnancy and Childbirth* 2021; **21**(1): 1-7·

17· Sulaiman S, Premji SS, Tavangar F, Yim IS, Lebold M· Total Adverse Childhood Experiences and Preterm Birth: A Systematic Review· *Maternal and Child Health Journal* 2021: 1-14·

18· Nesari M, Olson JK, Vandermeer B, Slater L, Olson DM· Does a maternal history of abuse before pregnancy affect pregnancy outcomes? A systematic review with meta-analysis· *BMC pregnancy and childbirth* 2018; **18**(1): 1-11·
19· Shamseer L, Moher D, Clarke M, et al· Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation· *Bmj* 2015; **349**·
20· Stroup DF, Berlin JA, Morton SC, et al· Meta-analysis of observational studies in epidemiology: a proposal for reporting· *Jama* 2000; **283**(15): 2008-12·
21· https://www·nichd·nih·gov/health/topics/pregnancy·
22· Racine N, Devereaux C, Cooke JE, Eirich R, Zhu J, Madigan S· Adverse childhood experiences and maternal anxiety and depression: a meta-analysis· *BMC psychiatry* 2021; **21**(1): 1-10·
23· Shor E, Roelfs D, Vang ZM· The "Hispanic mortality paradox" revisited: meta-analysis and meta-regression of life-course differentials in Latin American and Caribbean immigrants' mortality· *Social Science & Medicine* 2017; **186**: 20-33·
24· Borenstein M, Higgins JPT, Hedges LV, Rothstein HR· Basics of meta-analysis: I2 is not an absolute measure of heterogeneity· *Research synthesis methods* 2017; **8**(1): 5-18·
25· Furuya-Kanamori L, Barendregt JJ, Doi SAR· A new improved graphical and quantitative method for detecting bias in meta-analysis· *International journal of evidence-based healthcare* 2018; **16**(4): 195-203·
26· Barendregt JJ, Doi SA· MetaXL user guide version 5·3· *EpiGear International Pty Ltd* 2016·
27· Fredriksen E, von Soest T, Smith L, Moe V· Patterns of pregnancy and postpartum depressive symptoms: Latent class trajectories and predictors· *Journal of Abnormal Psychology* 2017; **126**(2): 173·
28· Hantsoo L, Jašarević E, Criniti S, et al· Childhood adversity impact on gut microbiota and inflammatory response to stress during pregnancy· *Brain, behavior, and immunity* 2019; **75**: 240-50·
29· Howell KH, Miller-Graff LE, Schaefer LM, Scrafford KE· Relational resilience as a potential mediator between adverse childhood experiences and prenatal depression· *Journal of health psychology* 2020; **25**(4): 545-57·
30· Letourneau N, Dewey D, Kaplan BJ, et al· Intergenerational transmission of adverse childhood experiences via maternal depression and anxiety and moderation by child sex· *Journal of developmental origins of health and disease* 2019; **10**(1): 88-99·
31· Narayan AJ, Rivera LM, Bernstein RE, Harris WW, Lieberman AF· Positive childhood experiences predict less psychopathology and stress in pregnant women with childhood adversity: A pilot study of the benevolent childhood experiences (BCEs) scale· *Child abuse & neglect* 2018; **78**: 19-30·
32· Racine N, Zumwalt K, McDonald S, Tough S, Madigan S· Perinatal depression: the role of maternal adverse childhood experiences and social support· *Journal of affective disorders* 2020; **263**: 576-81·
33· Young-Wolff KC, Alabaster A, McCaw B, et al· Adverse childhood experiences and mental and behavioral health conditions during pregnancy: the role of resilience· *Journal of Women's Health* 2019; **28**(4): 452-61·
34· Christiaens I, Hegadoren K, Olson DM· Adverse childhood experiences are associated with spontaneous preterm birth: a case–control study· *BMC medicine* 2015; **13**(1): 1-9·
35· Mason SM, Tobias DK, Clark CJ, Zhang C, Hu FB, Rich-Edwards JW· Abuse in Childhood or Adolescence and Gestational Diabetes: a retrospective cohort study· *American journal of preventive medicine* 2016; **50**(4): 436-44·

36· McDonnell CG, Valentino K· Intergenerational effects of childhood trauma: evaluating pathways among maternal ACEs, perinatal depressive symptoms, and infant outcomes· *Child maltreatment* 2016; **21**(4): 317-26·
37· Appleton AA, Kiley K, Holdsworth EA, Schell LM· Social support during pregnancy modifies the association between maternal adverse childhood experiences and infant birth size· *Maternal and child health journal* 2019; **23**(3): 408-15·
38· Salah AB, Lemieux A, Mlouki I, et al· Impact of social violence and childhood adversities on pregnancy outcomes: a longitudinal study in Tunisia· *Journal of global health* 2019; **9**(2)·
39· Bhengu BS, Tomita A, Mashaphu S, Paruk S· The role of adverse childhood experiences on perinatal substance use behaviour in KwaZulu-Natal Province, South Africa· *AIDS and Behavior* 2020; **24**(6): 1643-52·
40· Shaikh K, Premji SS, Lalani S, et al· Ethnic disparity and exposure to supplements rather than adverse childhood experiences linked to preterm birth in Pakistani women· *Journal of Affective Disorders* 2020; **267**: 49-56·
41· Barrios YV, Gelaye B, Zhong Q, et al· Association of childhood physical and sexual abuse with intimate partner violence, poor general health and depressive symptoms among pregnant women· *PloS one* 2015; **10**(1): e0116609·
42· Mersky JP, Lee CP· Adverse childhood experiences and poor birth outcomes in a diverse, low-income sample· *BMC pregnancy and childbirth* 2019; **19**(1): 1-7·
43· Grimstad H, Schei B· Pregnancy and delivery for women with a history of child sexual abuse· *Child abuse & neglect* 1999; **23**(1): 81-90·
44· Noll JG, Schulkin J, Trickett PK, Susman EJ, Breech L, Putnam FW· Differential pathways to preterm delivery for sexually abused and comparison women· *Journal of pediatric psychology* 2007; **32**(10): 1238-48·
45· Leeners B, Rath W, Block E, Görres G, Tschudin S· Risk factors for unfavorable pregnancy outcome in women with adverse childhood experiences· *Journal of Perinatal Medicine* 2014; **42**(2): 171-8·
46· Selk SC, Rich-Edwards JW, Koenen K, Kubzansky LD· An observational study of type, timing, and severity of childhood maltreatment and preterm birth· *J Epidemiol Community Health* 2016; **70**(6): 589-95·
47· Harville EW, Boynton-Jarrett R, Power C, Hyppönen E· Childhood hardship, maternal smoking, and birth outcomes: a prospective cohort study· *Archives of pediatrics & adolescent medicine* 2010; **164**(6): 533-9·
48· Miller GE, Culhane J, Grobman W, et al· Mothers' childhood hardship forecasts adverse pregnancy outcomes: role of inflammatory, lifestyle, and psychosocial pathways· *Brain, behavior, and immunity* 2017; **65**: 11-9·
49· Cammack AL, Hogue CJ, Drews-Botsch CD, et al· An exploratory study of whether pregnancy outcomes influence maternal self-reported history of child maltreatment· *Child abuse & neglect* 2018; **85**: 145-55·
50· Bala K, Monteiro K, Martha K, High P· The Association between Adverse Childhood Experiences and Diabetes Status during Pregnancy among Women in Rhode Island, 2016-2018· *Rhode Island Medical Journal* 2020; **103**(9): 52-5·
51· Gillespie SL, Christian LM, Alston AD, Salsberry PJ· Childhood stress and birth timing among African American women: Cortisol as biological mediator· *Psychoneuroendocrinology* 2017; **84**: 32-41·
52· Smith MV, Gotman N, Yonkers KA· Early childhood adversity and pregnancy outcomes· *Maternal and child health journal* 2016; **20**(4): 790-8·

53· Ranchod YK, Headen IE, Petito LC, Deardorff JK, Rehkopf DH, Abrams BF· Maternal childhood adversity, prepregnancy obesity, and gestational weight gain· *American journal of preventive medicine* 2016; **50**(4): 463-9·
54· Schoenaker DAJM, Callaway LK, Mishra GD· The Role of Childhood Adversity in the Development of Gestational Diabetes· *American Journal of Preventive Medicine* 2019; **57**(3): 302-10·
55· Bhengu BS, Tomita A, Mashaphu S, Paruk S· The role of adverse childhood experiences on perinatal substance use behaviour in KwaZulu-Natal Province, South Africa· *AIDS and Behavior* 2019: 1-10·
56· Sadeghimahalli F, Zardooz H, Golchoobian R· Early postnatal hypothalamic-pituitary-adrenal axis activity and reduced insulin sensitivity in adult rats· *Endocrine regulations* 2019; **53**(4): 213-20·
57· Chen Y-T, Hu Y, Yang Q-Y, et al· Excessive glucocorticoids during pregnancy impair fetal brown fat development and predispose offspring to metabolic dysfunctions· *Diabetes* 2020; **69**(8): 1662-74·
58· Bick J, Nelson CA· Early adverse experiences and the developing brain· *Neuropsychopharmacology* 2016; **41**(1): 177-96·
59· Kornmeier J, Bach M· Ambiguous figures–what happens in the brain when perception changes but not the stimulus· *Frontiers in human neuroscience* 2012; **6**: 51·
60· Nusslock R, Miller GE· Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis· *Biological psychiatry* 2016; **80**(1): 23-32·
61· Danese A, McEwen BS· Adverse childhood experiences, allostasis, allostatic load, and age-related disease· *Physiology & behavior* 2012; **106**(1): 29-39·
62· Yaribeygi H, Panahi Y, Sahraei H, Johnston TP, Sahebkar A· The impact of stress on body function: A review· *EXCLI journal* 2017; **16**: 1057·
63· Hollingsworth K, Callaway L, Duhig M, Matheson S, Scott J· The association between maltreatment in childhood and pre-pregnancy obesity in women attending an antenatal clinic in Australia· *PLoS One* 2012; **7**(12): e51868·
64· Cornelius DC, Cottrell J, Amaral LM, LaMarca B· Inflammatory mediators: a causal link to hypertension during preeclampsia· *British journal of pharmacology* 2019; **176**(12): 1914-21·
65· Rodrigo N, Glastras SJ· The emerging role of biomarkers in the diagnosis of gestational diabetes mellitus· *Journal of clinical medicine* 2018; **7**(6): 120·
66· Leeners B, Richter-Appelt H, Imthurn B, Rath W· Influence of childhood sexual abuse on pregnancy, delivery, and the early postpartum period in adult women· *Journal of psychosomatic research* 2006; **61**(2): 139-51·
67· Wosu AC, Gelaye B, Williams MA· Maternal history of childhood sexual abuse and preterm birth: an epidemiologic review· *BMC pregnancy and childbirth* 2015; **15**(1): 1-9·
68· Adcock A, Bate, A·, & Woodhouse, J· (2016)· Effect of social media on the mental health of young people· Retrieved fromhttp://researchbriefings·parliament·uk/ResearchBriefing/Summary/CDP□2016-0196·
69· Sterling P· Allostasis: a new paradigm to explain arousal pathology· *Handbook of life stress, cognition and health* 1988·
70· McEwen BS· Protective and damaging effects of stress mediators: central role of the brain· *Dialogues in clinical neuroscience* 2006; **8**(4): 367·
71· Olson DM, Severson EM, Verstraeten BSE, Ng JWY, McCreary JK, Metz GAS· Allostatic load and preterm birth· *International journal of molecular sciences* 2015; **16**(12): 29856-74·

72· Dodd JM, Turnbull DA, McPhee AJ, Wittert G, Crowther CA, Robinson JS· Limiting weight gain in overweight and obese women during pregnancy to improve health outcomes: the LIMIT randomised controlled trial· *BMC pregnancy and childbirth* 2011; **11**(1): 1-5·
73· Poston L, Bell R, Croker H, et al· Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial· *The lancet Diabetes & endocrinology* 2015; **3**(10): 767-77·
74· in Pregnancy TIWM, Group C· Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials· *The BMJ* 2017; **358**·
75· Mishra K, Atkins DE, Gutierrez B, Wu J, Cousineau MR, Hempel S· Screening for adverse childhood experiences in preventive medicine settings: a scoping review· *Journal of Public Health* 2021: 1-10·
76· Gentry S, Paterson B· Does screening or routine enquiry for adverse childhood experiences (ACEs) meet criteria for a screening programme? A rapid evidence summary· *Journal of Public Health* 2021.

Figure-1: PRISMA diagram outlining the search strategy and selection of studies included in this review.

Figure-2: Association of any ACE exposure with risk of pregnancy complications

Figure-3: Association of any ACE exposure and adverse pregnancy outcomes

Supplemental information

Supplementary figure -1.1: Association of ≥ 4 ACEs and adverse pregnancy complications

Supplementary figure -1.2: Association of <4 ACEs and adverse pregnancy complications

Supplementary figure -1.3: Association of ACEs (continuous scale) and adverse pregnancy complications

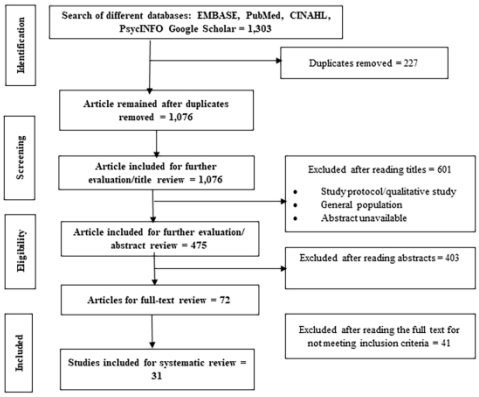
Supplementary figure -2.1: Association of ≥ 4 ACEs and adverse pregnancy outcomes

Supplementary figure -2.2: Association of <4 ACEs and adverse pregnancy outcomes

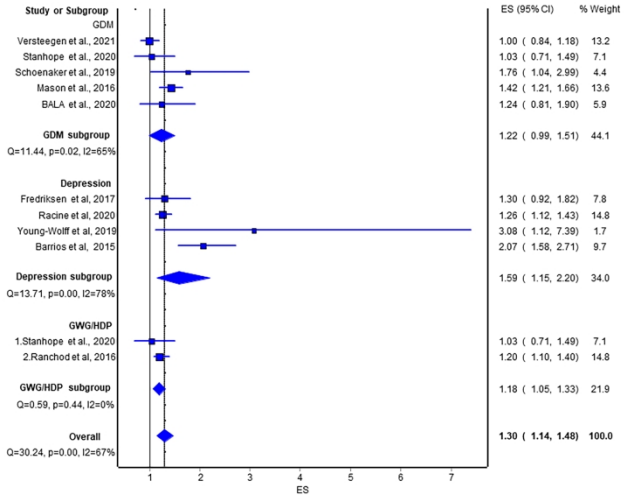
Supplementary figure -2.3: Association ACEs (continuous scale) and adverse pregnancy outcomes

Supplementary Table 1: Quality assessment tools

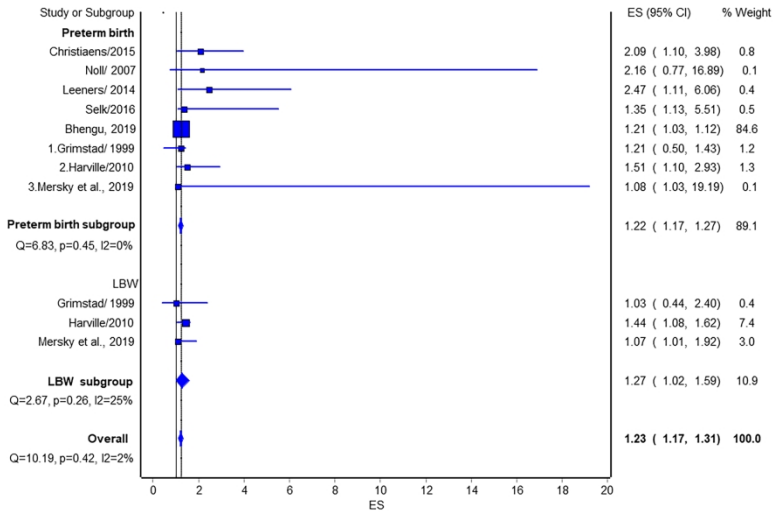
Supplementary Table 2: Quality of the study



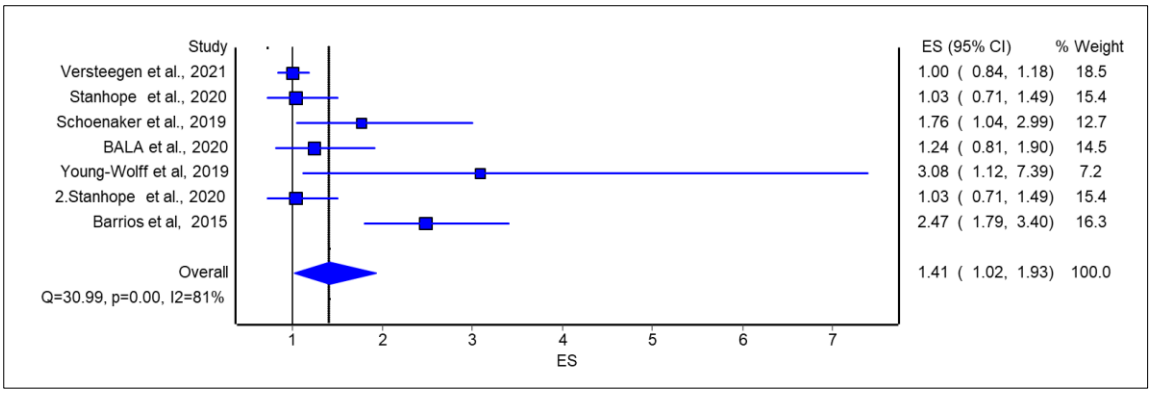
338x190mm (300 x 300 DPI)



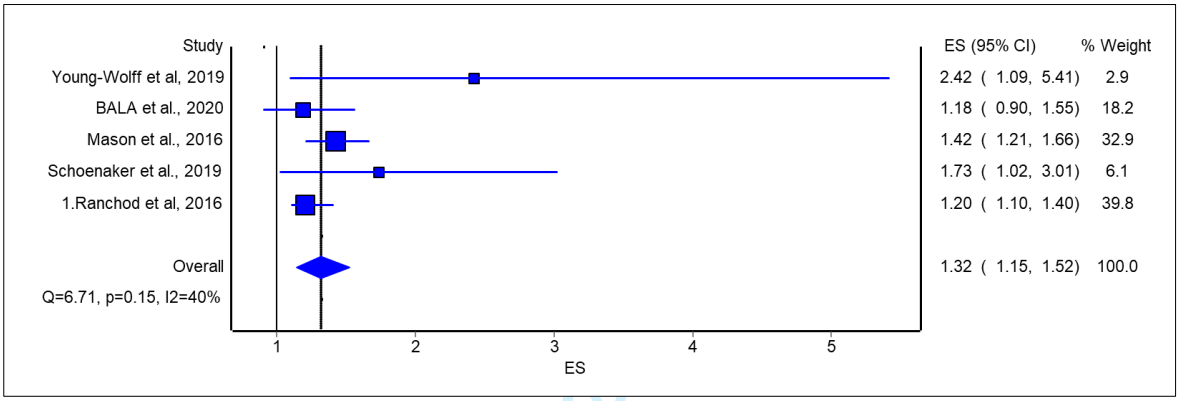
338x190mm (300 x 300 DPI)



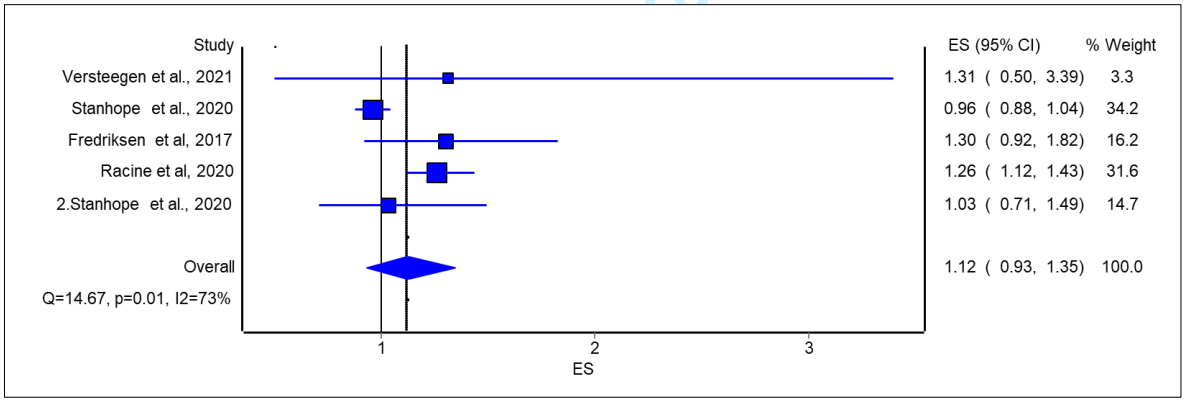
338x190mm (300 x 300 DPI)



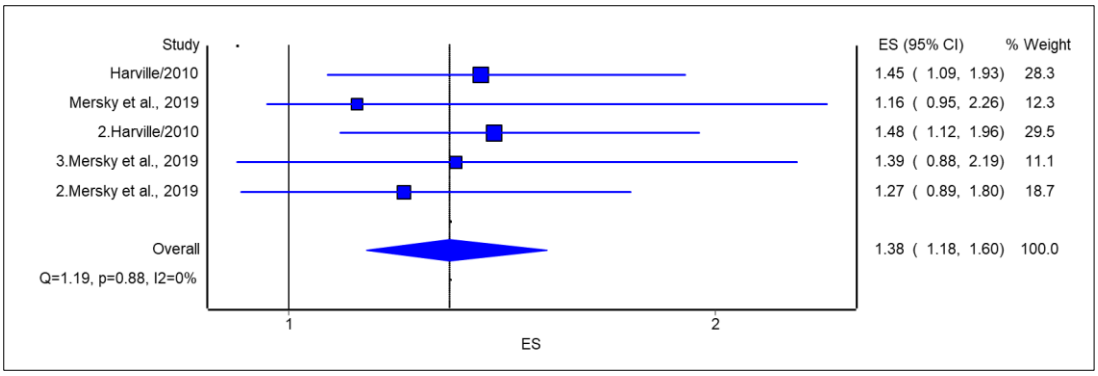
Supplementary figure -1.1: Association of ≥ 4 ACEs and adverse pregnancy complications



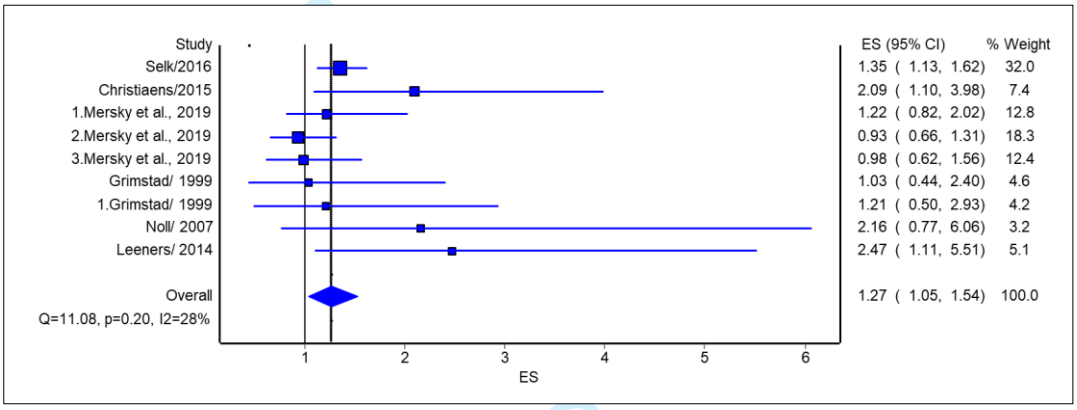
Supplementary figure -1.2: Association of <4 ACEs and adverse pregnancy complications



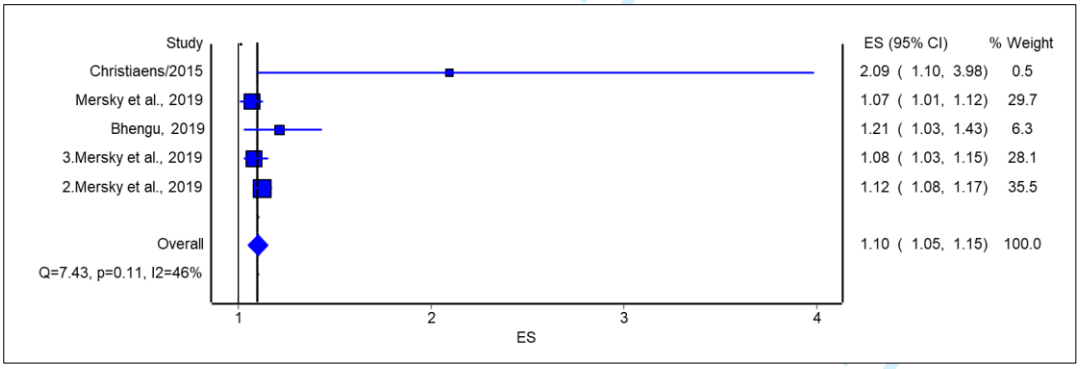
Supplementary figure -1.3: Association of ACEs (continuous scale) and adverse pregnancy complications



Supplementary figure -2.1: Association of ≥ 4 ACEs and adverse pregnancy outcomes



Supplementary figure -2.2: Association of <4 ACEs and adverse pregnancy outcomes



Supplementary figure -2.3: Association ACEs (continuous scale) and adverse pregnancy outcomes

Supplementary Table 1: Quality assessment tools

Study Quality Evaluation		
Item	**Question**	**Coding**
1. Question	Was the research question or objective in this paper clearly stated?	0-No 1-Yes
2. Population	Was the study population clearly specified and defined?	0-No 1-Yes
3. Participation	Was the participation rate of eligible persons at least 50%?	0-No 1-Yes
4. Inclusion/Exclusion Criteria	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	0-No 1-Yes
5. Sample Size	Was a sample size justification, power description, or variance and effect estimates provided?	0-No 1-Yes
6.	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	0-No 1-Yes
7. Timeframe	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	0-No 1-Yes
8. Levels of Exposure	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	0-No 1-Yes
9. Independent Variable	Were the exposure measures (independent variables) clearly defined, valid, reliable, and	0-No 1-Yes

	implemented consistently across all study participants?	
10. Longitudinal/Repeated ACEs	Was the exposure(s) assessed more than once over time?	0-No 1-Yes
11. Dependent Variable	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	0-No 1-Yes
12. Objectivity independent variable	Does the study use objective reports or multiple-methods to measure maternal ACEs? Objective measure = child abuse reports Multiple methods = self-report and corroborated reports.	0-self report 1-objective measure/multiple methods
13. Objective dependent variables	Does the study use different reporters or multiple-methods to measure maternal health/mental health outcomes? Objective measure = hospital report, diagnosis by physician, measurement by health care professional	0-self report 1-objective measure/multiple methods
14. Lost to Follow-Up	Was loss to follow-up after baseline 20% or less?	0-No 1-Yes
15. Confounder	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	0-No 1-Yes
Total	A sum of all items was calculated to obtain a total quality score (0-15).	

Supplementary Table 2: Quality of the study

SI#	First Author/Pub Date	Question	Population	Participation	Inclusion/Exclusion Criteria	Sample Size	Exposures	Timeframe	Levels of Exposure	Independent Variable	Longitudinal/Repeated ACEs	Dependent Variable	Objectivity independent variable	Objective dependent variables	Lost to Follow-Up	Confounder	Overall
1	Christiaens/2015	1	1	0	1	1	1	1	1	1	0	0	1	0	0	1	10
2	Grimstad/ 1999	1	1	1	1	1	1	1	0	0	0	0	1	1	0	0	9
3	Stevens- Simon/1994	1	1	1	0	0	1	1	0	0	0	0	1	1	0	0	7
4	Noll/ 2007	1	1	1	0	0	1	1	0	0	0	0	1	1	0	0	7
5	Leeners/ 2014	0	1	1	0	0	1	0	0	0	0	0	0	0	0	1	10
6	Selk/2016	1	**1**	1	1	1	1	1	1	1	0	1	1	1	0	1	13
7	Harville/2010	1	1	1	0	1	1	1	1	1	1	1	0	1	0	1	12
8	Rich-Edwards et al., 2010	1	**1**	1	1	1	1	1	1	1	0	1	1	1	0	1	13
9	Versteegen et al., 2021	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14
10	Stanhope et al., 2020	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14
11	Schoenaker et al., 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14
12	Miller et al., 2017	1	1	1	1	1	1	0	0	1	0	1	0	1	0	0	9
13	Mersky et al., 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13
14	Mason et al., 2016	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13
15	Cammack et al., 2018	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13
16	BALA et al., 2020	1	1	1	1	1	1	1	0	1	0	1	1	1	0	1	12
17	Ben Salah et al, 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13
18	Bhengu, 2019	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	12
19	Gillespie et al. (2017)	1	1	1	0	1	1	1	0	1	1	1	1	0	0	0	10
20	Leeners et al, 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15
21	McDonnell and Val et al, 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	14
22	Shaikh et al., 2019	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	11
23	Smith et al., 2016	1	1	1	1	0	0	1	1	1	0	1	0	0	1	1	10
24	Ranchod et al, 2016	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	8
25	Appleton et al, 2019	1	1	1	1	0	0	1	0	1	0	1	0	1	1	0	9
26	Fredriksen et al, 2017	1	1	1	1	0	0	1	1	1	0	1	0	0	0	0	8
27	Hantsoo et al,2019	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	8
28	Letourneau et al, 2019	1	1	1	1	0	0	1	1	1	0	1	0	0	1	1	10

29	Mersky et al, 2018	1	1	1	1	0	1	1	1	1	1	1	0	0	1	1	12
30	Narayan et al, 2018	1	1	1	1	0	0	1	1	1	0	1	0	0	1	0	9
31	Racine et al, 2020	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	8
32	Young-Wolff et al, 2019	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	11
33	Barrios et al, 2015	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	11

Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-14
		(b) Give reasons for non-participation at each stage	8-14
		(c) Consider use of a flow diagram	8-14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-14
		(b) Indicate number of participants with missing data for each variable of interest	8-14
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-14
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8-14
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8-14
		Cross-sectional study—Report numbers of outcome events or summary measures	8-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-14
		(*b*) Report category boundaries when continuous variables were categorized	8-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

BMJ Open

Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-063826.R1
Article Type:	Original research
Date Submitted by the Author:	07-Dec-2022
Complete List of Authors:	Mamun, Abdullah; The University of Queensland Biswas, Tuhin; University of Queensland, Scott, James; University of Queensland Sly, P.D.; University of Queensland, Queensland Childrens Medical Research Instit McIntyre, David; Mater Research Institute The University of Queensland Thorpe , Karen ; University of Queensland Boyle , Frances; University of Queensland Dekker, N; University of Queensland, Centre for Clinical Research Doi, Suhail; Qatar University, Population Medicine Mitchell, Murray; QUT, Faculty of Health, School of Biomedical Sciences McNeil, Keith; Queensland Health Kothari, Alka ; University of Queensland Hardiman, Leah; Queensland Health Callaway, Leonie Kaye; Queensland Health
Primary Subject Heading:	Global health
Secondary Subject Heading:	Public health, Mental health, Health policy
Keywords:	Epidemiology < TROPICAL MEDICINE, EPIDEMIOLOGY, Adverse events < THERAPEUTICS, Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, Prenatal diagnosis < OBSTETRICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Author's names: Abdullah Al Mamun, PhD[1,2], Tuhin Biswas, PhD[1,2]; James G. Scott, PhD[3,4,5]; Peter D Sly, MD, DSc[6]; David McIntyre,PhD[7]; Karen Thorpe,PhD[1,2];Frances M. Boyle,PhD[1];Marloes Dekker Nitert PhD[8], Suhail A. R. Doi, PhD[9,10];Murray Mitchell, PhD[11]; Keith McNeil, PhD[12]; Alka Kothari, MD FRANZCOG[13,14], Leah Hardiman MSC[15], Leonie Callaway, PhD[15]

Author affiliations:

1. UQ Poche Centre for Indigenous Health, The University of Queensland, Queensland, Australia.
2. ARC Centre of Excellence for Children and Families over the Life Course, The University of Queensland, QLD, Australia
3. Mental Health Research Program, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia
4. Metro North Mental Health, Royal Brisbane and Women's Hospital, Herston, QLD, Australia
5. Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, QLD, Australia
6. Children's Health and Environment Program, Child Health Research Centre, The University of Queensland, QLD, Australia

7. Mater Research, Faculty of Medicine, University of Queensland, Mater Health, QLD, Australia.
8. School of Chemistry and Molecular Biosciences, The University of Queensland, QLD, Australia
9. Research School of Population Health, Australian National University, Canberra, Australian Capital Territory
10. Department of Population Medicine, College of Medicine, Qatar University, Doha
11. Faculty of Health, School of Biomedical Sciences, The Queensland University of Technology, QLD, Australia
12. Prevention Division, Queensland Health, QLD, Australia
13. Department of Obstetrics & Gynaecology, Redcliffe Hospital, Anzac Avenue, Redcliffe, QLD, Australia
14. Faculty of Medicine, The University of Queensland, QLD, Australia
15. Women's and Children's Stream - Metro North Hospital and Health Services, QLD, Australia
16. Institute for Social Science Research, The University of Queensland, QLD, Australia
17. Asian University for Women (AUW), Chittagong, Bangladesh
18.

Corresponding author:

Abdullah Al Mamun

UQ Poche Centre for Indigenous Health, The University of Queensland, Queensland, Australia.

74 High Street, Queensland 4068, Australia·

Email: mamun@sph.uq.edu.au

Telephone: +61 7 336 53163

Abstract

Background:

Adverse childhood experiences (ACEs) have a profound negative impact on health. However, the strength of the association between ACEs and pregnancy complications and adverse pregnancy outcomes is not well quantified or understood.

Objectives:

Conduct a systematic review and meta-analysis of the association between ACEs and risk of pregnancy complications and adverse pregnancy outcomes.

Search Strategy:

A comprehensive search was conducted using PubMed, EMBASE, CINAHL, PsycINFO, ClinicalTrials.gov and Google scholar up to July 2022.

Data Collection and Analysis:

Two reviewers independently conducted the screening and quality appraisal using a validated tool. Meta-analysis using the quality-effects model on the reported odds ratio (OR) was conducted. Heterogeneity and inconsistency were examined using the I^2 statistics.

Results:

Thirty-two studies from 1,508 met a priori inclusion criteria for systematic review, with 21 included in the meta-analysis. Pooled analyses showed that exposure to ACEs increased the

risk of pregnancy complications (odds ratio, OR=1·37, 95% CI: 1·20-1.50) and adverse pregnancy outcomes (OR=1·31, 95% CI: 1·16-1·48). In sub-group analysis, maternal ACEs were associated with gestational diabetes mellitus (OR=1·39, 95% CI: 1.11-1·74), antenatal depression (OR=1·59, 95% CI: 1·15-2·20), low offspring birth weight (OR=1·27, 95% CI: 1·02-1·59), and preterm delivery (OR=1·41, 95% CI: 1·16-1·71).

Conclusion:

The results suggest that exposure to ACEs increase the risk of pregnancy complications and adverse pregnancy outcomes. Preventive strategies, screening and trauma-informed care need to be examined to improve maternal and child health.

Funding statement: Not applicable

Keywords: Adverse childhood experiences, pregnancy complications, adverse pregnancy outcomes

Tweetable abstract:

Adverse childhood experiences linked to pregnancy complications and adverse pregnancy outcomes

Strengths and limitations of this study

- Maternal ACEs were associated with an increased risk of pregnancy complications, including GDM, GWG, HDP and depression/anxiety during pregnancy.
- ACE exposure showed a significant association with any adverse pregnancy outcome.
- Most of the included studies are from high-income western countries. Due to the lack of data, we could not conduct the ACEs item-specific analysis.
- The dose-response relationship in all studies could not be assessed as different studies use different screening tools and cut-off values.

Introduction

Adverse Childhood Experiences (ACEs)[1] are psychosocial stressors and traumas experienced by an individual before 18 years of age[2, 3] The pioneering study by Fellitti and colleagues (1998) demonstrated that exposure to ACEs is common, ACEs co-occur and that exposure to multiple ACEs are associated with an increased risk of health risk behaviours and illnesses.[4] Subsequently, a growing body of research has continued to provide consistent evidence that ACEs are a major public health issue due to their high prevalence and harmful effects that ACEs have on human health throughout life. [5, 6]

Early life experiences are recognized as essential determinants for health outcomes later in life especially in pregnant women and their children. [7] Adverse health outcomes in pregnancy can then result in intergenerational transmission of adverse health outcomes. Perhaps this occurs because women who have experienced ACEs may be a vulnerable group for development of health risk behaviours, including smoking, drug and alcohol use and sedentary lifestyle, along with consequences of trauma such as poor sleep.[5] These behaviours increase the risk of pregnancy complications including gestational diabetes mellitus (GDM), hypertensive disorder of pregnancy (HDP), excess gestational weight gain (GWG),

depression/anxiety during pregnancy [8] and adverse pregnancy outcomes including low birth weight and preterm birth.[9-11] Systematic reviews have reported women who had experienced child maltreatment are more likely to have pregnancy complications and that physical abuse and household substance abuse were associated with greater risk of GDM[12, 13] resulting in intergenerational transmission of adverse health outcomes. Overall, those reporting exposure to multiple ACEs (mostly 4 or more) have an increased risk of physical, mental, and substance use disorders. [14]

There is little information about ACEs and the associated risk of pregnancy complications and adverse birth outcomes. A longitudinal study in Australia reported that women exposed to three or more ACEs had an elevated GDM risk.[15] In contrast, a longitudinal study from the USA reported no significant association between ACEs (for each score change and reported 4 or more ACEs) and GDM.[16] A systematic review suggests that total ACEs (score in continuous scale) are associated with preterm birth, although this finding needs to be confirmed in other studies to explore the associations between ACEs and preterm birth using appropriate and valid instruments.[17] Another systematic review and meta-analysis reported that maternal history of abuse before pregnancy was significantly associated with preterm delivery and low birth weight.[18] No systematic review and meta-analysis has investigated the association of ACEs and the risk of pregnancy complications including GDM, HDP, GWG, depression/anxiety during pregnancy and adverse pregnancy outcomes. This study aims to systematically review and meta-analyse existing studies to establish the extent of association between ACEs and pregnancy complications and adverse birth outcomes. Understanding these associations will inform maternal clinical care and support for offspring of those women exposed to ACEs.

Methods

In this systematic review and meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [19] and the Meta-Analysis of Observational Studies in Epidemiology protocol [20] to ensure all necessary steps were followed. In accordance with the guidelines, the systematic review and meta-analysis protocol was registered in PROSPERO (CRD42021278030).

Literature search strategy

Our search included studies published to July 2022 using PubMed, EMBASE, CINAHL, PsycINFO, ClinicalTrials.gov and Google scholar. The search strategy employed with PubMed is: ((((((((((("adverse childhood experiences") OR ("childhood adversities")) OR ("childhood abuse")) OR ("childhood maltreatment")) OR ("child trauma")) OR ("adverse childhood events")) OR ("childhood sexual abuse")) OR ("childhood physical abuse")) OR ("childhood mental abuse")) OR ("childhood trauma")) OR ("childhood violence")) OR ("childhood hardship")) OR ("childhood suffering")) OR ("childhood Stress")) AND ((((((((((("pregnancy complications") OR ("Depression")) OR ("Anxiety")) OR ("Prenatal depression")) OR ("Depressive symptoms")) OR ("Antenatal depression")) OR ("Mental health problem")) OR ("gestational diabetes mellitus")) OR ("GDM")) OR ("hypertensive disorder of pregnancy")) OR ("HDP")) OR ("preeclampsia")) OR ("maternal body weight")) OR ("excess weight gain")) OR ("abnormal fetal growth")) OR ("Intrauterine growth restriction")) OR ("Low birth weight")) OR (LBW)) OR (IUGR)) OR (Stillbirth)) OR ("small of gestational age")) OR ("preterm birth")). This search details are presented in a supplementary table (Table S1).

Inclusion criteria

Studies were included if the full-text was published in English, population was pregnant women, reported any ACEs including childhood maltreatment (childhood physical, emotional and sexual abuse, childhood physical and emotional neglect and exposure to parental intimate partner violence), childhood trauma or childhood hardship/suffering and if studies reported any pregnancy-related complications according to National Institute of Health (NIH)[21] (GDM, HDP, GWG, depression/anxiety during pregnancy) and adverse birth outcomes such as low birth weight, intra-uterine growth restriction (IUGR), preterm birth, stillbirth. Studies were excluded if: (1) published in languages other than English; (2) included general population (not pregnant); (3) reported reviews, qualitative studies, editorials, abstracts, case reports and letters to the editor or (4) explored violence during pregnancy.

Data extraction

Two independent reviewers (TB and AAM) carried out the data extraction. If AAM and TB did not reach agreement, the small group (AAM, TB, LC and JS) discussed discrepancies to reach a consensus. A similar approach was used for title/abstract and full text reviews. Relevant data from each of the selected studies was extracted including first author; study title; country of study; sample size; study design; types of ACEs; measurement scale; and outcomes (both risk of pregnancy complications and adverse pregnancy outcomes) and recorded on an Excel spreadsheet.

Quality assessment

Fifteen-point scale quality assessment tools were used to assess the quality and risk of bias of the studies. We adapted a quality assessment tool from NIH “Quality Assessment Tool for

Observational Cohort and Cross-sectional studies".[22] This tool allowed assessment of the question, population, participation, inclusion/exclusion criteria, sample size, exposures, timeframe, levels of exposure, independent variables, longitudinal/repeated ACEs, dependent variable, objectively measured independent variables, objectively measured dependent variables, lost to follow-up and confounders (**Supplementary** Table S2). Overall quality score was considered as a continuous variable for bias adjustment in the pooled estimates. However, we have also categorised the overall quality score into three groups: 13-15 as high; 10-12 as moderate and <10 as low.

The results of the quality assessment are presented in **Supplementary** Table S3.

Data Analysis

Meta-analysis conducted in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines. Analyses focused on the overall association between ACEs and risk of pregnancy complications and adverse birth outcomes. Subgroup data synthesis was performed only when three or more studies were available with the estimates for a similar type of ACE exposures. ACE scores were considered on the continuous scale (for each unit change) and three categories: i) none versus one ACEs; ii) two to three ACEs (low ACEs); and (iii) four or more ACEs (high ACEs). Although most of the studies reported the odds ratio (OR) as the measurement of association between exposures and outcomes, two studies reported relative risk (RR) and one hazard ratio (HR). We converted all measures of associations into ORs using conversion methods reported elsewhere. [23] In the meta-analysis, we used the quality effects model (QE) [24] for bias adjustment. The advantage of the QE model is that the between-study variability is adjusted based on the relative quality rank of the studies instead of on random variables assigned by the random effect (RE) model. The heterogeneity of the studies was reported by the I-squared value (I2) that measures the proportion of total variance between studies beyond random error.[24] We checked for publication bias through visualization by funnel plot and Doi plot.[25] All the analyses were conducted using the MetaXL software version 5.3.[26]

Patient and Public Involvement

None

Data sharing

This is a systematic review of literature. All the data extracted from the literature is available on reasonable request.

Results

The literature search resulted in 1,508 records, which were screened for duplication (n=398), review of titles (n=1,086) and further abstract evaluation (n=485). Finally, 32 studies met our inclusion criteria for systematic review, and 21 were included in meta-analysis **(Figure 1)**. 75% of the studies were cohort studies and the remainder were either cross sectional or case-control studies. The majority of the studies were conducted in the USA (n = 19), with fewer studies from Canada (n=3), Europe (n=6) and other regions (n=5). The study sample sizes varied from 48 to 11,556. The publication year ranged from 1994 to 2022. Thirteen studies used the 10-item ACEs questionnaire[8, 16, 27-37], three used World Health Organization (WHO) ACE-IQ questionnaires[38-40] with one study used 8-items [41] and two studies used 19-items questionnaire[42, 43] and fourteen studies used other measures [35, 44-55] **(Table-1)**.

232 **Table-1: Characteristics of studies included in the systematic review and meta-analysis**

SI#	First Author/Pub Date	Country	Study design	Sample size	Measurement scale
1	Christiaens/2015	Canada	Case-control	622	10-item self-report tool by Felliti et al
2	Grimstad/ 1999	Norway	Case-control	174	Were asked about the character of the experience(s): Genital Touch; Forced to touch the other person's genitals; Attempted Coitus; 4. Penile Vaginal Coitus
3	Noll/ 2007	USA	Cohort	186	Childhood sexual abuse
4	Leeners/ 2014	Switzerland	Cohort	255	Childhood sexual abuse experiences were additionally explored using questions modified by Wyatt
5	Selk/2016	USA	Case-control	51434	The measure of physical abuse included items from the Revised Conflict Tactics Scale (CTS); The sexual abuse measure was derived from the survey by Finkelhor et al
6	Harville/2010	UK	Cohort	4865	The phrase "childhood hardship" is used herein to refer to a num-ber of adverse situations in childhood: • Financial/structural hardship • No interest in education • Family dysfunction • Lack of supportive caregiving • Violence/mental health issues • Issues of family structure • No. of hardships
7	Appleton et al, 2019	USA	Cohort study	126	10-item self-report tool by Felliti et al
8	Versteegen et al., 2021	USA	Cohort	30	10-item self-report tool by Felliti et al
9	Stanhope et al., 2020	USA	Cohort	2319	10-item self-report tool by Felliti et al
10	Schoenaker et al., 2019	Australia	Cohort	11,556	10-item self-report tool by Felliti et al
11	Miller et al., 2017	USA	Prospective study	744	asked women a series of questions about their family's conditions during childhood
12	Mersky et al., 2019	USA	Longitudinal	1848	19-item assessment that has demonstrated good internal consistency
13	Mason et al., 2016	USA	Cohort	45,550	Physical abuse and Sexual abuse

14	Cammack et al., 2018	USA	Cohort	230	Childhood Trauma Questionnaire Short-Form (CTQ)
15	BALA et al., 2020	Rhode Island	Population-based survey	3350	7-item questionnaire
16	Ben Salah et al, 2019	Tunesia	Prospective follow-up study	593	ACE-International Questionnaire (ACE-IQ)
17	Bhengu, 2019	South Africa	cross-sectional	223	WHO-ACE IQ
18	Gillespie et al. (2017)	USA	Prospective observational design	89	The Stress and Adversity Inventory (STRAIN)
19	Leeners et al, 2014	Switzerland	cohort	225	using questions modified from a questionnaire developed by Wyatt
20	McDonnell et al, 2014	USA	Cohort	398	10-item self-report tool by Felliti et al
21	Shaikh et al., 2019	Pakistan	Cohort	300	World Health Organization 31-item ACEs –
22	Smith et al., 2016	USA	Cohort	2303	The main modification of the instrument was to collapse the sexual events before the age of 18 questions into 1 question asking about childhood sexual abuse prior to age 18.
23	Ranchod et al, 2016	USA	Longitudinal study	2,873	4-Item questionnaire
24	Fredriksen et al, 2017	Norway	Cohort	762	10-item self-report tool by Felliti et al
25	Hantsoo et al,2019	USA	Observational study	48	10-item self-report tool by Felliti et al
26	Howell1,2019	USA	Observational study	101	10-item self-report tool by Felliti et al
27	Letourneau et al, 2019	Canada	Cohort	907	10-item self-report tool by Felliti et al
28	Narayan et al, 2018	USA	Cohort	101	10-item self-report tool by Felliti et al
29	Racine et al, 2020	Canada	Cohort	1994	10-item self-report tool by Felliti et al
30	Young-Wolff et al, 2019	USA	Cohort	355	10-item self-report tool by Felliti et al
31	Barrios et al, 2015	USA	Cohort	1,521	Eight questions from CDC
32	Hardcastle et al., 2022	UK	Cross sectional	865	10-item self-report tool by Felliti et al

In total, 32 studies were included for quality assessment. Eleven studies (34.38%) were assessed as high quality, 12 studies (37.50%) were assessed as moderate quality, and 9 studies (28.13%) were assessed as poor quality (Table S3).ACEs and risk of pregnancy complications

ACEs and GDM: Six studies[8, 16, 35, 36, 51, 56] described an association between ACEs and GDM and only one study reported (**Table-2.1)**. there was no association between ACEs and GDM [42]. A large epidemiological study in Australia [56] reported that, in pregnant women, exposure to any three ACEs (adjusted relative risk, aRR=1.73, 95% CI:1·0, 3·0) or four or more ACEs (aRR=1·70, 95% CI:1·00, 2·90) was associated with elevated GDM risk after adjusting preconception BMI, unhealthy diet, parity, and maternal age. Another study in the USA by Mason et al., 2016[35] reported that both moderate (adjusted odds ratio, aOR=1·08, 95% CI:0.96, 1·22) and severe (aOR=1.42, 95% CI:1·21, 1·66) childhood physical abuse was associated with an increased risk of GDM. This study also reported that forced sexual activity during childhood was associated with an increased risk of GDM (aOR 1·30, 95% CI:1·14, 1·49).

ACEs, GWG and HDP: Only one study by Ranchod et al., 2016[54] examined the association between ACEs and GWG. They found that exposure to physical abuse and household alcohol abuse were independently associated with a 20% increase in the risk of excessive GWG. A study by Stanhope et al., 2020[8] found that for each ACEs score, there was a slight increase in the HDP risk (aOR=1·03, 95% CI:0·71, 1·49), although it was not statistically significant. However, they found that physical abuse (aOR= 1·22, 95% CI: 1·10-1·42) and household alcohol abuse (aOR= 1·21, 95% CI: 1·11-1·32) were associated with a significant increase in the risk of excessive GWG (**Table-2.1)**.

Table-2.1: Summary of published measures of effect.

1	Appleton et al, 2019	Depression	ACE's score (continuous)	Pearson's correlations coefficients (0.37)
2	Versteegen et al., 2021	GDM	ACEs total	1.05 (0.98, 1.14)
			ACEs binary	2.85 (1.15-7.06)
3	Stanhope et al., 2020	GDM	ACEs 4+	1.03 (0.71, 1.49)
			Continuous ACE score	0.96 (0.88, 1.04)
		HDP	ACEs 4+	1.03 (0.71, 1.49)
			Continuous ACE score:	1.03 (0.71, 1.49)
4	Schoenaker et al., 2019	GDM	Three ACEs	1.73, (1.02, 3.01)
			Four or more ACEs	1.76, (1.04, 2.99)
5	Mason et al., 2016	GDM	Mild physical abuse	1.08 (0.96, 1.22)
			Moderate physical abuse	11.16 (1.04, 1.29)
			Severe physical abuse	1.42 (1.21, 1.66).
			Forced sexual activity	1.30 (1.14, 1.49)
			Combine	1.42, (1.21, 1.66)
6	BALA et al., 2020	GDM	3 or more ACEs	1.24, (0.81–1.90)
			1–2 ACEs	1.18, (0.90– 1.55)
7	McDonnell et al, 2014	GDM		GDM not correlated with ACE indicators
8	Ranchod et al, 2016	GWG	Physical abuse	1.2, (1.1-1.4)
			Household alcohol abuse	1.2, (1.1-1.3)
			Household mental illness	1.1, (0.9-1.2).
9	Fredriksen et al., 2017	Depression	ACEs continuous	1.3, (0.92-1.82)
10	Hantsoo et al.,2019	Depression	< 2 ACES	EPDS (Median [IQR]): 5 [3, 6]
			2 or more ACES	EPDS (Median [IQR]): 3 [1.5, 6.0]
11	Howell et al., 2020	Depression	ACEs continuous	Adverse childhood experiences had a direct effect on depression, B=1.11, standard error=.44, p=.01,
12	Letourneau et al, 2019	Depression	ACEs continuous	Maternal ACEs were associated with symptoms of anxiety and depression during pregnancy
13	Narayan et al et al., 2018	Depression	ACEs continuous	Maternal ACEs were associated with depression during pregnancy ($\beta = 0.32$, $p < 0.01$).
14	Racine et al et al., 2020	Depression	ACEs continuous	1.26, (1.12-1.43)
15	Young-Wolff et al et al., 2019	Depression	3+ ACEs	3.08, (1.12-7.39)
			1–2 ACEs	2.42 (1.09–5.41)
16	Barrios et al., 2015	Depression		Depression: OR: 2.07; 95% CI: 1.58-2.71

ACEs and depression/anxiety: Nine studies[27-33, 37, 41] examined the association between ACEs and depression/anxiety with almost all studies reporting a significant positive association during pregnancy (**Table-2.1)**. For example, a large cohort study in Canada by Racine et al, 2020[32] reported that ACEs were associated with depressive symptoms in pregnancy (aOR =1·26, 95% CI :1·12–1·43). Another study by Letourneau et al, 2019[30] reported that for each maternal ACE, there was an increased risk of symptoms of anxiety and depression during pregnancy. An observational study in the USA by Hantsoo et al[28, 29] reported that ACEs directly affected depression (B=1·1, standard error=·44, p=·01).

Meta-analytic results for maternal ACEs and risk of pregnancy complications:

A total of 11 studies (72,889 participants) were available for the quality-effect meta-analysis, which produced an association between maternal any ACEs and risk of any adverse pregnancy complications (OR=1·37, 95% CI: 1·20-1·57) **(Figure-2)**. In risk factor-specific sub-analysis, five studies (7116 participants) were available for meta-analysis, which produced a moderate association between maternal ACEs and risk of GDM (OR=1·39, 95% CI: 1.11-1·74). For depression/anxiety during pregnancy, four studies (6116 participants) were available for this meta-analysis, which produced an association between maternal ACEs and risk of depression/anxiety during pregnancy (OR=1·5, 95% CI: 1·15-2·2). Both low (OR=1·30, 95% CI: 1·10-1·50) and high (OR=1·41, 95% CI: 1·02-1·90) number of ACEs were associated with and pregnancy complications (**Supplementary** Figure S1**.1 and 1.2**).

ACEs and adverse pregnancy outcomes

ACEs and preterm birth: Out of 31 studies, 12 [34, 38, 40, 42-48, 50, 55, 57] reported the association between ACEs and preterm birth(**Table-2.2)**. A study in Tunisia by Ben Salah et

al. (2019) reported that after adjustment for high-risk pregnancies, environmental tobacco smoke, and intra-familial ACEs, the risk of premature birth was significantly associated with exposure to collective violence (P-value < 0.001) and witnessing community violence (P-value < 0·05). In another study, Harville et al[48] reported that violence exposure during childhood was associated with a 44% increased risk of preterm birth (adjusted RR= 1·40; 95% CI: 1·00-1·90). They also found the family mental health issues increased by 24%, and a 25% increase in the risk of preterm birth. A case-control study in the USA by Selk et al[47] reported that women exposed to forced sex during childhood had a 22% greater risk of preterm birth (adjusted RR=1·2, 95% CI: 1·10-1·30) than those in the no exposure group. Furthermore, exposure to physical and sexual abuse during childhood was associated with a 35% greater risk of preterm birth (adjusted RR=1·30, 95% CI: 1·10-1·60). A study by Miller et al., reported that mothers' childhood economic hardship was independently associated with multiple adverse birth outcomes.[49] A study by Gillespie et al reported that maternal childhood abuse was associated with birth timing (birth timing was operationalized as a days gestation at birth continuous variable and calculated according to obstetric estimate of date of delivery and actual date of delivery extracted from the prenatal and labor and delivery records). [52]

ACEs and low birth weight:

Out of 31 studies, six [38, 42, 44, 48, 50, 53] reported an association between ACEs and low birth weight (**Table-2.2)**.

303 **Table-2.2: Summary of published measures of effect.**

SI#	First Author/Pub Date	Outcomes	Types of ACEs and analytical unit	Findings (OR, 95% CI)
1	Christiaens et al., 2015	Preterm birth	High ACE score (≥2 ACE)	2.09, (1.10–3.98)
			ACE's score (continuous)	1.18, (0.99–1.40)
2	Grimstad et al.,1999	Preterm birth	Sexual Abuse	1.03, (0.44-2.4)
		Low birth weight	Sexual Abuse	1.21, (0.5-2.93)
3	Noll et al., 2007	Preterm birth	Sexual abuse	2.16, (0.77-6.06)
4	Leeners et al., 2014	Preterm birth	Sexual abuse	2.47, (1.11-5.51)
5	Selk et al., 2016	Preterm birth	Severe physical only	1.02, (0.88- .17)
			Forced sex only	1.22, (1.1-1.35)
			Experienced both severe abuse types	1.35, (1.13-1.62)
6	Harville et al., 2010	Preterm birth	Financial/structural hardship	1.20 (0.90-1.60)
			No interest in education	1.17 (0.93-1.48)
			Family dysfunction	1.20 (0.94-1.52)
			Lack of supportive caregiving	0.98 (0.81-1.19)
			Violence/mental health issues	1.24 (0.94-1.63)
			Issues of family structure	1.25 (1.02-1.54)
			No. of hardships (≥ 4)	1.45 (1.09-1.93)
		Low birth weight	Financial/structural hardship	1.18 (0.88-1.60)
			No interest in education:	1.18 (0.88-1.60)
			Family dysfunction	1.18 (0.88-1.60)
			Lack of supportive caregiving	1.18 (0.88-1.60)
			Violence/mental health issues	1.48 (1.12-1.96)
			Issues of family structure	1.48 (1.12-1.96)
			No. of hardships (≥ 4)	1.48 (1.12-1.96)
11	Miller et al., 2017	Birth outcomes	Childhood economic hardship	Mother's hardship independently associated with multiple adverse birth outcomes
12	Mersky et al., 2019	Preterm birth	ACE scores (continuous)	1.07, (1.01–1.12)
			1 or 2 ACEs	1.22 (0.79–1.89)
			3 or 4 ACEs	1.29 (0.82–2.02)
			5 or more ACEs	1.46 (0.95–2.26)
		Low birthweight	ACE scores (continuous)	1.08, (1.03–1.15)
			1 or 2 ACEs	0.98 (0.62–1.56)
			3 or 4 ACEs	1.22 (0.76–1.96)
			5 or more ACEs	1.39 (0.88–2.19)
		Pregnancy loss	ACE scores (continuous)	1.12, (1.08–1.17)
			1 or 2 ACEs	0.93 (0.66–1.31)
			3 or 4 ACEs	1.27 (0.89–1.80)
			5 or more ACEs	1.27 (0.89–1.80)
14	Cammack et al., 2018	Low Birth Weight	Emotional Abuse	0.88 (0.66–1.00) Cohen's Kappas (95% CI)
			Physical Abuse	0.50 (0.01–0.99)
			Sexual Abuse	0.75 (0.43–1.00)
			Emotional Neglect	0.59 (0.18–1.00)
			Physical Neglect	0.28 (−0.16–0.73)

		Preterm Birth	Emotional Abuse	0.78 (0.55–1.00)
			Physical Abuse	0.69 (0.36–1.00)
			Sexual Abuse	0.78 (0.55–1.00)
			Emotional Neglect	0.44 (0.12–0.77)
			Physical Neglect	0.39 (−0.03–0.81)
		NICU Admission	Emotional Abuse	0.58 (0.25–0.91)
			Physical Abuse	0.28 (−0.15–0.71)
			Sexual Abuse	0.73 (0.45–1.00)
			Emotional Neglect	0.55 (0.20–0.90)
			Physical Neglect	0.55 (0.20–0.90)
16	Ben Salah et al, 2019	Preterm Birth Low birth weight	ACEs continuous	After adjustment for high-risk pregnancies, environmental tobacco smoke, and intra-familial ACEs, the risk of premature birth was significantly associated with exposure to collective violence (P < 0.001) and witnessing community violence (P < 0.05).
17	Bhengu et al., 2019	Preterm Birth	ACEs continuous	1.21, (1.03-1.43)
18	Gillespie et al. (2017)	Birth timing	ACEs continuous	Cumulative childhood stress predicted birth timing (p = 0.01).
19	Leeners et al, 2014	Preterm Birth		CSA, physical abuse as well as other ACE were associated with an increased risk for premature delivery
21	Shaikh et al., 2019	Preterm Birth	ACEs continuous	We found no association between ACE and preterm birth
22	Smith et al., 2016	Birth weight and shorter gestational age	ACEs continuous	Each additional ACE decreased birth weight by 16.33 g and decreased gestational age by 0.063.
32	Hardcastle et al., 2022	Preterm Birth	1 ACE	0.80 (0.32-2.00)
			2–3 ACEs	1.17 (0.46-2.97)
			≥4 ACEs	2.67 (1.14-6.23)

304

305

Harville et al reported that violence exposure during childhood was associated with an increased risk of low birth weight (adjusted OR= 1·5; 95% CI: 1·1-2·0). They also found that violence/mental health issues (adjusted OR=1·4, 95% CI:1·1-1·9) and issues of family structure increased the risk of low birth weight (adjusted OR=1·4, 95% CI:1·1-1·9). A study by Smith et al. reported that each additional ACE decreased gestational age at birth as well as birth weight. [53]

Meta-analytic results for maternal ACEs and adverse pregnancy outcomes:

A total of 12 studies were available for this quality-effects meta-analysis, which produced an association between maternal ACEs and any adverse pregnancy outcomes (OR=1·31, 95% CI: 1·17-1·47). In a sub-analysis of eight studies (59,607 participants), the quality-effects meta-analysis showed an association between maternal ACEs and preterm birth (OR=1·41, 95% CI: 1·16-1·71). On the other hand, three studies (7,014 participants) were available for the quality-effects meta-analysis for low birth weight, which showed an association between maternal ACEs and low birth weight (OR=1·27, 95% CI: 1·17-1·47) **(Figure-3)**. In low (one to three ACEs) and high (four+) ACEs specific analysis, five studies reported low ACEs exposure and nine studies reported high ACEs exposure. Both low (OR=1·27, 95% CI: 1·05-1·54) and high (OR=1·41, 95% CI: 1·20-1·65) ACE exposure showed a significant association with any adverse pregnancy outcome. For each additional unit increase in the number of ACEs, the odds of adverse pregnancy outcomes increased 1.10 times **(**OR=1·10, 95% CI: 1·05-1·15) (**Supplementary figure** S2.1 and 2.2).

Discussion

This systematic review and meta-analysis found that maternal ACEs were associated with an increased risk of pregnancy complications including GDM, HDP, GWG and mental health

during pregnancy. Similarly, this study also found that maternal ACEs were associated with an increased risk of adverse pregnancy outcomes including preterm birth and low birth weight. All these associations were stronger for 4 or more compared to less than 4 ACEs. There was a dose-response association between ACEs and adverse pregnancy outcome. Overall, findings of this study suggest there is a robust association between ACEs and pregnancy complications and adverse pregnancy outcomes. Early prevention of ACEs might reduce the risk of pregnancy complications and adverse outcomes.

To our knowledge, this is the first systematic review and meta-analysis to assess the association between ACEs and pregnancy complications and adverse pregnancy outcomes. A recent systematic review and meta-analysis reported an association between ACEs and maternal depression and/or anxiety in the perinatal period (pregnancy to 1-year postpartum). [22] though the results of our study are not directly comparable to this study because outcomes were considered at different perinatal windows and results were presented differently (e.g., effect size vs. odds ratio). Our results on maternal ACEs and increased risk of adverse pregnancy outcomes are more comprehensive than previous systematic reviews [58] [59] [18] due to the availability of 12 recent primary studies. Overall, the direction and strength of the associations in our study is similar to these earlier studies [58] [59] [18].

There could be several potential direct and indirect pathways to explain the relationship between ACEs and pregnancy complications and adverse pregnancy outcomes. Direct mechanisms may include altering the regulation of stress-signalling pathways [60] and immune system function[61]; changing brain structure and function; and changing the expression of DNA and by accelerating cellular ageing[62].For example, abuse or neglect might directly lead to malnutrition. Similarly, stress can directly lead to dysregulation of the hypothalamicpituitary-adrenal axis and associated neuro-endocrine-immune[63] as well as epigenetic effects[64]. Results from animal models [65, 66] and longitudinal human studies

such as the Nurses' Health Study [35] have proposed that a strong history of ACEs may alter hypothalamic-pituitary-adrenal axis as reflected by elevated cortisol levels that in turn alter glucose metabolism and body weight regulation. Brain development begins in fetal life and continues into early adulthood. Early life maternal ACEs may alter the structure and function of the brain.[67, 68] These neurodevelopmental alterations may result in neuroendocrine disruption of cortisol regulation, linked to glucose metabolism [69, 70]. The experience of ACEs increased the risk of physical or sexual abuse during pregnancy and is associated with placental damage, uterine contractions, premature rupture of membranes, and genitourinary infections which ultimately increase the risk of preterm birth and low birth weight[71]. Exposure to ACEs is also associated with an increased risk of health risk behaviours including substance use, physical inactivity and unhealthy diet[4]. Previous research has shown that ACEs are associated with pre-pregnancy obesity.[72] In addition, it is also established that socioeconomic status and cumulative disadvantage produces health disparities across the life course[73]. Any of these mechanisms could explain the transgenerational nature of obesity and diabetes in families affected by maternal ACEs. Chronic inflammation, unhealthy behaviours, poor sleep and altered stress regulatory pathways are risk factors for adverse pregnancy complications, including GDM, HDP and depression/anxiety [74, 75]. The interplay of these different pathways remains largely unclear.

According to our findings and other systematic review evidence, it may be valuable to assess the role of routine ACEs screening during pregnancy to improve maternal and child health. Trauma-informed care is not well incorporated into clinical practice guidelines. Much of the emphasis in maternity care is on individual behaviour change, including advice about diet, exercise, smoking cessation and uptake of clinical care. Approaches that do not incorporate the personal experiences of trauma by women attending antenatal services may inadvertently cause

iatrogenic harm. For many years, there has been an interest in improving pregnancy outcomes by focusing on a limited set of physical parameters that can easily be measured such as gestational weight gain, without attention to the underlying mechanisms.[76, 77] Overall, studies of diet and exercise in pregnancy to reduce GDM, HDP and other adverse pregnancy outcomes have been disappointing.[78]

A recent scoping review by Tran et al.[79] found that healthcare providers perceive that they are not being trained to screen for ACEs in their undergraduate training program or in their professional training in clinical settings. In addition, healthcare workers already have a high demand on their time and limited capacity to incorporate new practices without additional resources. There is some controversy about whether screening for ACEs is a safe and ethical practice, especially if the consequences of discussing ACEs (e.g. effects on mental health) cannot be readily addressed[80, 81]. These identified barriers are similar to those reported by healthcare providers in relation to ACE screening in general clinical settings[82]. Healthcare providers may appreciate the importance of asking about ACEs to help raise issues that otherwise would be unknown and unaddressed[79]. , Furthermore, Mishra et al[83] found that ACEs screening did not excessively disrupt clinic workflow. and was both acceptable for the patient and feasible for the provider. However, to determine if screening for ACEs is worthwhile, studies need to assess if trauma-informed clinical care translates to improved clinical outcomes for mother and offspring. [84] Beyond screening for ACEs, our findings emphasise the importance of preventing ACEs in children to reduce immediate impacts as well as intergenerational transmission of ACEs. As well as supporting clinicians and providing services to address ACEs, there is growing awareness of the crucial role of upstream policy- and community-level interventions to improve and support positive family and social environments and a need for wide-scale testing of the effectiveness of such interventions[85][86].

There are some limitations to the current study, which reduce the generalisability of the findings. Firstly, most of the included studies are from high-income western countries. Secondly, due to the lack of data, we could not conduct the ACEs item-specific analysis. Thirdly, the dose-response relationship in all studies could not be assessed as different studies use different screening tools and cut-off values. Only five studies exploring pregnancy complications and five studies investigating adverse pregnancy outcomes could be assessed for a dose response relationship. Lastly, as we considered various types of ACE exposures in a single review, we expected much heterogeneity in the study methodologies, populations, exposures, and outcome identification. To address these limitations, the Quality Effect model, which incorporates the heterogeneity of effects across the studies and reduces the risk-of-bias assessment was used in the meta-analysis. Nevertheless, our study has several strengths considering the comprehensive nature of the inclusion criteria, including relevant studies published up to July 2021. In addition, we assessed the methodological quality of studies using standard tools appropriate for observational cohort and cross-sectional studies.

Conclusion

In conclusion, this systematic review and meta-analysis found that exposure to ACEs increases the risk of pregnancy complications and adverse pregnancy outcomes. Identification of women exposed to ACEs and personalising their care may provide opportunities to improve maternal and child mental and physical health.

Contribution to authorship

AAM and TB contributed towards literature search, data analysis and interpretation, figures and tables, and writing of the manuscript. AAM, TB, LC, JS, PS contributed towards the drafting of the protocol, review of the study design, data collection and interpretation and provided a critical review of the manuscript. AAM and SD contributed towards data

management and analysis plan and provided oversight and interpretation of the analyses. AAM, DM, KT, FB, MN, MM, KM, AK, LH contributed towards the study design and editing. AAM and LC contributed towards the design of the manuscript, development of the protocol, and critical evaluation and interpretation of the results and critical review of the manuscript.

Disclosure of interests

All other authors declare no competing interests.

Details of ethics approval

None

Funding

None

Acknowledgement

This research was partially supported by the Australian Research Council Centre of Excellence for Children and Families over the Life Course.

445

446

Figure-1: PRISMA diagram outlining the search strategy and selection of studies included in this review.

Figure-2: Association of any ACE exposure with risk of pregnancy complications

Figure-3: Association of any ACE exposure and adverse pregnancy outcomes

References:

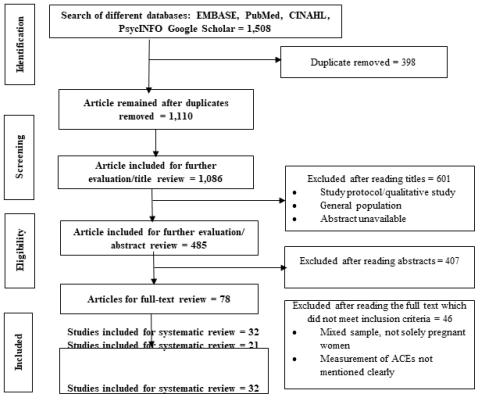
1. Atzl, V.M., et al., *Adverse childhood experiences and prenatal mental health: Type of ACEs and age of maltreatment onset.* Journal of family psychology, 2019. **33**(3): p. 304.
2. Hughes, K., et al., *The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis.* The Lancet Public Health, 2017. **2**(8): p. e356-e366.
3. Wickramasinghe, Y.M., et al., *Burden of adverse childhood experiences in children attending paediatric clinics in South Western Sydney, Australia: a retrospective audit.* BMJ paediatrics open, 2019. **3**(1).
4. Felitti, V.J., et al., *Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study.* American journal of preventive medicine, 1998. **14**(4): p. 245-258.
5. Petruccelli, K., J. Davis, and T. Berman, *Adverse childhood experiences and associated health outcomes: A systematic review and meta-analysis.* Child abuse & neglect, 2019. **97**: p. 104127.
6. Schroeder, K., et al., *The association between adverse childhood experiences and childhood obesity: A systematic review.* Obesity Reviews, 2021. **22**(7): p. e13204.
7. Kuh, D., et al., *Life course epidemiology.* Journal of epidemiology and community health, 2003. **57**(10): p. 778.
8. Stanhope, K.K., et al., *Adverse childhood experiences and lifetime adverse maternal outcomes (gestational diabetes and hypertensive disorders of pregnancy) in the Hispanic Community Health Study/Study of Latinos.* Annals of Epidemiology, 2020. **50**: p. 1-6.
9. Schetter, C.D. and L. Tanner, *Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice.* Current opinion in psychiatry, 2012. **25**(2): p. 141.
10. Olsen, J.M., *Integrative review of pregnancy health risks and outcomes associated with adverse childhood experiences.* Journal of Obstetric, Gynecologic & Neonatal Nursing, 2018. **47**(6): p. 783-794.
11. Dachew, B.A., et al., *Association between hypertensive disorders of pregnancy and the development of offspring mental and behavioural problems: a systematic review and meta-analysis.* Psychiatry research, 2018. **260**: p. 458-467.
12. Montgomery, E., C. Pope, and J. Rogers, *A feminist narrative study of the maternity care experiences of women who were sexually abused in childhood.* Midwifery, 2015. **31**(1): p. 54-60.
13. Montgomery, E., C. Pope, and J. Rogers, *The re-enactment of childhood sexual abuse in maternity care: a qualitative study.* BMC pregnancy and childbirth, 2015. **15**(1): p. 1-7.
14. Lê-Scherban, F., et al., *Intergenerational associations of parent adverse childhood experiences and child health outcomes.* Pediatrics, 2018. **141**(6).
15. Schoenaker, D.A., L.K. Callaway, and G.D. Mishra, *The role of childhood adversity in the development of gestational diabetes.* American journal of preventive medicine, 2019. **57**(3): p. 302-310.
16. Versteegen, M., et al., *Maternal depression, adverse childhood experiences, and social support in relation to gestational diabetes risk: results from the Albany Infant and Mother Study (AIMS).* BMC Pregnancy and Childbirth, 2021. **21**(1): p. 1-7.
17. Sulaiman, S., et al., *Total Adverse Childhood Experiences and Preterm Birth: A Systematic Review.* Maternal and Child Health Journal, 2021: p. 1-14.
18. Nesari, M., et al., *Does a maternal history of abuse before pregnancy affect pregnancy outcomes? A systematic review with meta-analysis.* BMC pregnancy and childbirth, 2018. **18**(1): p. 1-11.
19. Shamseer, L., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.* Bmj, 2015. **349**.
20. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting.* Jama, 2000. **283**(15): p. 2008-2012.

21. https://www.nichd.nih.gov/health/topics/pregnancy.
22. Racine, N., et al., *Adverse childhood experiences and maternal anxiety and depression: a meta-analysis.* BMC psychiatry, 2021. **21**(1): p. 1-10.
23. Shor, E., D. Roelfs, and Z.M. Vang, *The "Hispanic mortality paradox" revisited: meta-analysis and meta-regression of life-course differentials in Latin American and Caribbean immigrants' mortality.* Social Science & Medicine, 2017. **186**: p. 20-33.
24. Borenstein, M., et al., *Basics of meta-analysis: I2 is not an absolute measure of heterogeneity.* Research synthesis methods, 2017. **8**(1): p. 5-18.
25. Furuya-Kanamori, L., J.J. Barendregt, and S.A.R. Doi, *A new improved graphical and quantitative method for detecting bias in meta-analysis.* International journal of evidence-based healthcare, 2018. **16**(4): p. 195-203.
26. Barendregt, J.J. and S.A. Doi, *MetaXL user guide version 5.3.* EpiGear International Pty Ltd, 2016.
27. Fredriksen, E., et al., *Patterns of pregnancy and postpartum depressive symptoms: Latent class trajectories and predictors.* Journal of Abnormal Psychology, 2017. **126**(2): p. 173.
28. Hantsoo, L., et al., *Childhood adversity impact on gut microbiota and inflammatory response to stress during pregnancy.* Brain, behavior, and immunity, 2019. **75**: p. 240-250.
29. Howell, K.H., et al., *Relational resilience as a potential mediator between adverse childhood experiences and prenatal depression.* Journal of health psychology, 2020. **25**(4): p. 545-557.
30. Letourneau, N., et al., *Intergenerational transmission of adverse childhood experiences via maternal depression and anxiety and moderation by child sex.* Journal of developmental origins of health and disease, 2019. **10**(1): p. 88-99.
31. Narayan, A.J., et al., *Positive childhood experiences predict less psychopathology and stress in pregnant women with childhood adversity: A pilot study of the benevolent childhood experiences (BCEs) scale.* Child abuse & neglect, 2018. **78**: p. 19-30.
32. Racine, N., et al., *Perinatal depression: the role of maternal adverse childhood experiences and social support.* Journal of affective disorders, 2020. **263**: p. 576-581.
33. Young-Wolff, K.C., et al., *Adverse childhood experiences and mental and behavioral health conditions during pregnancy: the role of resilience.* Journal of Women's Health, 2019. **28**(4): p. 452-461.
34. Christiaens, I., K. Hegadoren, and D.M. Olson, *Adverse childhood experiences are associated with spontaneous preterm birth: a case–control study.* BMC medicine, 2015. **13**(1): p. 1-9.
35. Mason, S.M., et al., *Abuse in Childhood or Adolescence and Gestational Diabetes: a retrospective cohort study.* American journal of preventive medicine, 2016. **50**(4): p. 436-444.
36. McDonnell, C.G. and K. Valentino, *Intergenerational effects of childhood trauma: evaluating pathways among maternal ACEs, perinatal depressive symptoms, and infant outcomes.* Child maltreatment, 2016. **21**(4): p. 317-326.
37. Appleton, A.A., et al., *Social support during pregnancy modifies the association between maternal adverse childhood experiences and infant birth size.* Maternal and child health journal, 2019. **23**(3): p. 408-415.
38. Salah, A.B., et al., *Impact of social violence and childhood adversities on pregnancy outcomes: a longitudinal study in Tunisia.* Journal of global health, 2019. **9**(2).
39. Bhengu, B.S., et al., *The role of adverse childhood experiences on perinatal substance use behaviour in KwaZulu-Natal Province, South Africa.* AIDS and Behavior, 2020. **24**(6): p. 1643-1652.
40. Shaikh, K., et al., *Ethnic disparity and exposure to supplements rather than adverse childhood experiences linked to preterm birth in Pakistani women.* Journal of affective disorders, 2020. **267**: p. 49-56.
41. Barrios, Y.V., et al., *Association of childhood physical and sexual abuse with intimate partner violence, poor general health and depressive symptoms among pregnant women.* PloS one, 2015. **10**(1): p. e0116609.

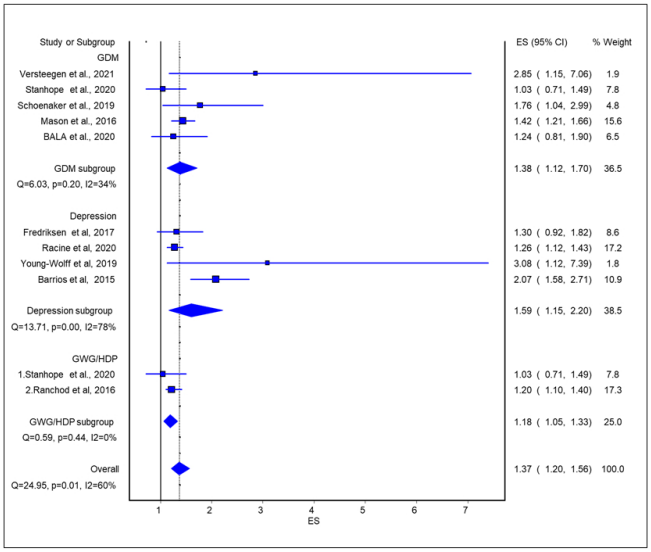
42. Mersky, J.P. and C.P. Lee, *Adverse childhood experiences and poor birth outcomes in a diverse, low-income sample.* BMC pregnancy and childbirth, 2019. **19**(1): p. 1-7.
43. Do, H.P., et al., *Intergenerational effects of violence on women's perinatal wellbeing and infant health outcomes: evidence from a birth cohort study in Central Vietnam.* BMC pregnancy and childbirth, 2021. **21**(1): p. 1-14.
44. Grimstad, H. and B. Schei, *Pregnancy and delivery for women with a history of child sexual abuse.* Child abuse & neglect, 1999. **23**(1): p. 81-90.
45. Noll, J.G., et al., *Differential pathways to preterm delivery for sexually abused and comparison women.* Journal of pediatric psychology, 2007. **32**(10): p. 1238-1248.
46. Leeners, B., et al., *Risk factors for unfavorable pregnancy outcome in women with adverse childhood experiences.* Journal of Perinatal Medicine, 2014. **42**(2): p. 171-178.
47. Selk, S.C., et al., *An observational study of type, timing, and severity of childhood maltreatment and preterm birth.* J Epidemiol Community Health, 2016. **70**(6): p. 589-595.
48. Harville, E.W., et al., *Childhood hardship, maternal smoking, and birth outcomes: a prospective cohort study.* Archives of pediatrics & adolescent medicine, 2010. **164**(6): p. 533-539.
49. Miller, G.E., et al., *Mothers' childhood hardship forecasts adverse pregnancy outcomes: role of inflammatory, lifestyle, and psychosocial pathways.* Brain, behavior, and immunity, 2017. **65**: p. 11-19.
50. Cammack, A.L., et al., *An exploratory study of whether pregnancy outcomes influence maternal self-reported history of child maltreatment.* Child abuse & neglect, 2018. **85**: p. 145-155.
51. Bala, K., et al., *The Association between Adverse Childhood Experiences and Diabetes Status during Pregnancy among Women in Rhode Island, 2016-2018.* Rhode Island Medical Journal, 2020. **103**(9): p. 52-55.
52. Gillespie, S.L., et al., *Childhood stress and birth timing among African American women: Cortisol as biological mediator.* Psychoneuroendocrinology, 2017. **84**: p. 32-41.
53. Smith, M.V., N. Gotman, and K.A. Yonkers, *Early childhood adversity and pregnancy outcomes.* Maternal and child health journal, 2016. **20**(4): p. 790-798.
54. Ranchod, Y.K., et al., *Maternal childhood adversity, prepregnancy obesity, and gestational weight gain.* American journal of preventive medicine, 2016. **50**(4): p. 463-469.
55. Hardcastle, K., K. Ford, and M.A. Bellis, *Maternal adverse childhood experiences and their association with preterm birth: secondary analysis of data from universal health visiting.* BMC pregnancy and childbirth, 2022. **22**(1): p. 1-11.
56. Schoenaker, D.A.J.M., L.K. Callaway, and G.D. Mishra, *The Role of Childhood Adversity in the Development of Gestational Diabetes.* American Journal of Preventive Medicine, 2019. **57**(3): p. 302-310.
57. Bhengu, B.S., et al., *The role of adverse childhood experiences on perinatal substance use behaviour in KwaZulu-Natal Province, South Africa.* AIDS and Behavior, 2019: p. 1-10.
58. Leeners, B., et al., *Influence of childhood sexual abuse on pregnancy, delivery, and the early postpartum period in adult women.* Journal of psychosomatic research, 2006. **61**(2): p. 139-151.
59. Wosu, A.C., B. Gelaye, and M.A. Williams, *Maternal history of childhood sexual abuse and preterm birth: an epidemiologic review.* BMC pregnancy and childbirth, 2015. **15**(1): p. 1-9.
60. *Elwenspoek MMC, Kuehn A, Muller CP, Turner JD. The effects of early life adversity on the immune system. Psychoneuroendocrinology 2017;82:140-54.*
61. *Bick J, Zhu T, Stamoulis C, Fox NA, Zeanah C, Nelson CA. Effect of early institutionalization and foster care on long-term white matter development: a randomized clinical trial. JAMA Pediatr 2015;169:211-9.*
62. *Marini S, Davis KA, Soare TW, et al. Adversity exposure during sensitive periods predicts accelerated epigenetic aging in children. Psychoneuroendocrinology 2020;113:104484.*

63. Danese, A., *The hidden wounds of childhood trauma: Psychoneuroimmunology of early stress and the impact on mental health.* Brain and Neuroscience Advances, 2017. **1**: p. 345-346.
64. *Thaler L, Steiger H. Eating disorders and epigenetics. Adv Exp Med Biol 2017;978:93-103. .*
65. Sadeghimahalli, F., H. Zardooz, and R. Golchoobian, *Early postnatal hypothalamic-pituitary-adrenal axis activity and reduced insulin sensitivity in adult rats.* Endocrine regulations, 2019. **53**(4): p. 213-220.
66. Chen, Y.-T., et al., *Excessive glucocorticoids during pregnancy impair fetal brown fat development and predispose offspring to metabolic dysfunctions.* Diabetes, 2020. **69**(8): p. 1662-1674.
67. Bick, J. and C.A. Nelson, *Early adverse experiences and the developing brain.* Neuropsychopharmacology, 2016. **41**(1): p. 177-196.
68. Kornmeier, J. and M. Bach, *Ambiguous figures–what happens in the brain when perception changes but not the stimulus.* Frontiers in human neuroscience, 2012. **6**: p. 51.
69. Nusslock, R. and G.E. Miller, *Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis.* Biological psychiatry, 2016. **80**(1): p. 23-32.
70. Danese, A. and B.S. McEwen, *Adverse childhood experiences, allostasis, allostatic load, and age-related disease.* Physiology & behavior, 2012. **106**(1): p. 29-39.
71. Adcock, A., Bate, A., & Woodhouse, J. (2016). Effect of social media on the mental health of young people. Retrieved fromhttp://researchbriefings.parliament.uk/ResearchBriefing/Summary/CDP2016-0196.
72. Hollingsworth, K., et al., *The association between maltreatment in childhood and pre-pregnancy obesity in women attending an antenatal clinic in Australia.* PLoS One, 2012. **7**(12): p. e51868.
73. Seabrook, J.A. and W.R. Avison, *Socioeconomic status and cumulative disadvantage processes across the life course: implications for health outcomes.* Canadian Review of Sociology/Revue canadienne de sociologie, 2012. **49**(1): p. 50-68.
74. Cornelius, D.C., et al., *Inflammatory mediators: a causal link to hypertension during preeclampsia.* British journal of pharmacology, 2019. **176**(12): p. 1914-1921.
75. Rodrigo, N. and S.J. Glastras, *The emerging role of biomarkers in the diagnosis of gestational diabetes mellitus.* Journal of clinical medicine, 2018. **7**(6): p. 120.
76. Dodd, J.M., et al., *Limiting weight gain in overweight and obese women during pregnancy to improve health outcomes: the LIMIT randomised controlled trial.* BMC pregnancy and Childbirth, 2011. **11**(1): p. 1-5.
77. Poston, L., et al., *Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial.* The lancet Diabetes & endocrinology, 2015. **3**(10): p. 767-777.
78. in Pregnancy, T.I.W.M. and C. Group, *Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials.* The BMJ, 2017. **358**.
79. *Tran, N, Callaway L, Shen S, Biswas T, Scott J, Boyle F, Mamun AA. Screening for adverse childhood experiences in antenatal care settings: A scoping review. Aust N Z J Obstet Gynaecol. 2022 Jul 31. doi: 10.1111/ajo.13585. .*
80. *Gillespie RJ. Screening for Adverse Childhood Experiences in Pediatric Primary Care: Pitfalls and Possibilities. Pediatr Ann. 2019 Jul 1;48(7):e257-e261.*
81. *Campbell, T. L. (2020). Screening for adverse childhood experiences (ACEs) in primary care: A cautionary note. JAMA, 323(23), 2379-2380.*
82. *Ereyi-Osas Whitney, Racine Nicole, Sheri M. Asking about adverse childhood experiences (ACEs) in prenatal and pediatric primary care: A Narrative Review and Critique 2020.*
83. Mishra, K., et al., *Screening for adverse childhood experiences in preventive medicine settings: a scoping review.* Journal of Public Health, 2021: p. 1-10.

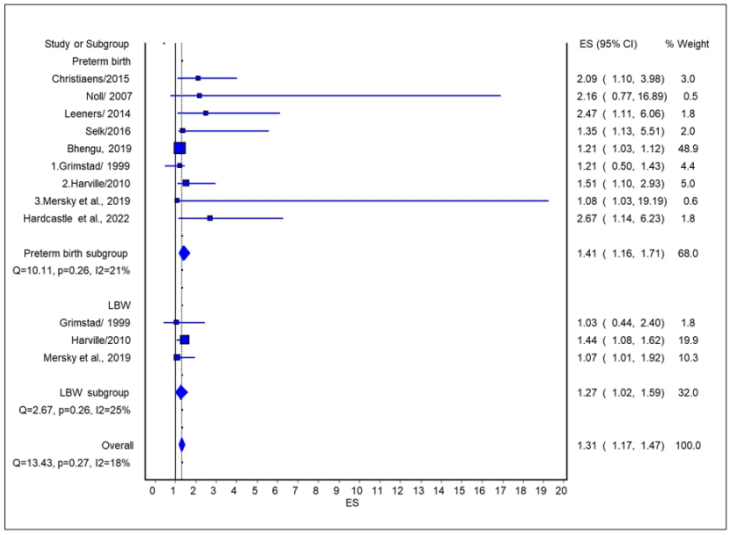
84. Gentry, S. and B. Paterson, *Does screening or routine enquiry for adverse childhood experiences (ACEs) meet criteria for a screening programme? A rapid evidence summary.* Journal of Public Health, 2021.
85. Courtin, E., et al., *The role of socioeconomic interventions in reducing exposure to Adverse Childhood Experiences: A systematic review.* Current Epidemiology Reports, 2019. **6**(4): p. 423-441.
86. Gervin, D.W., et al., *Centers for Disease Control and Prevention investments in adverse childhood experience prevention efforts.* American Journal of Preventive Medicine, 2022. **62**(6): p. S1-S5.



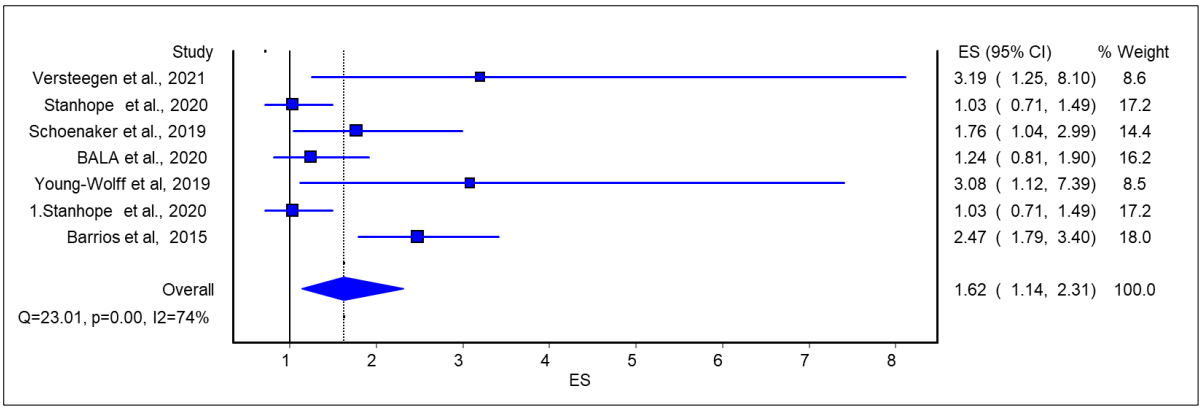
338x190mm (96 x 96 DPI)



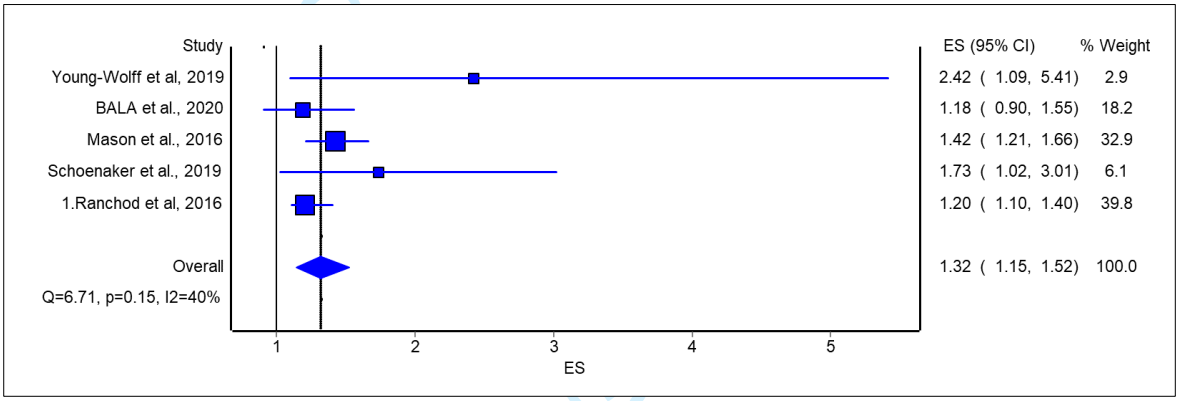
338x190mm (96 x 96 DPI)



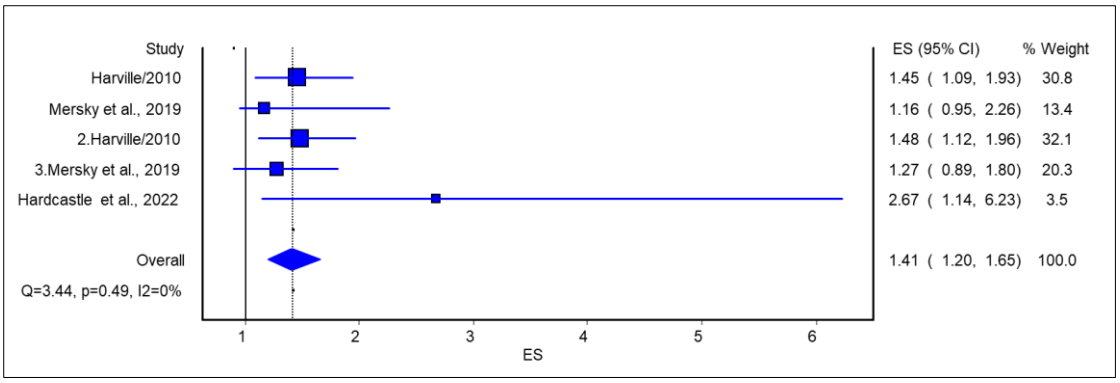
338x190mm (96 x 96 DPI)



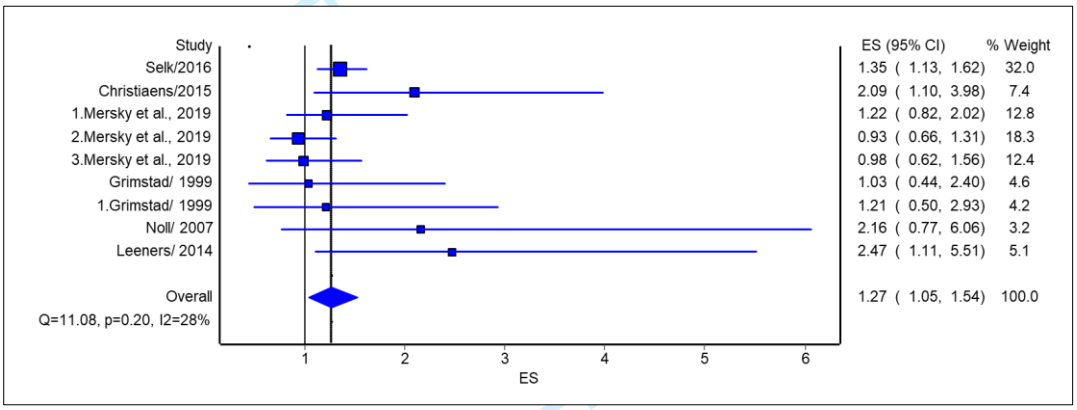
Supplementary figure -1.1: Association of ≥ 4 ACEs and adverse pregnancy complications



Supplementary figure -1.2: Association of <4 ACEs and adverse pregnancy complications



Supplementary figure -2.1: Association of ≥ 4 ACEs and adverse pregnancy outcomes



Supplementary figure -2.2: Association of <4 ACEs and adverse pregnancy outcomes

Supplementary Table S1: Search details

	#	
ACES	1	'Adverse childhood experiences'/exp OR 'adverse childhood experiences'
	2	'Childhood adversities'
	3	'Childhood abuse'
	4	'Childhood maltreatment'
	5	'Child trauma'
	6	'Adverse childhood events'
	7	'Childhood sexual abuse'
	8	'Childhood physical abuse'
	9	'Childhood mental abuse'
	10	'Childhood trauma'
	11	'Childhood violence'
	12	'Childhood hardship'
	13	'Childhood suffering'
	14	'Childhood stress'
	15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
Pregnancy complications	16	'Pregnancy complications'
	17	'depression'
	18	'anxiety'
	19	'Prenatal depression'
	20	'Depressive symptoms'
	21	'Antenatal depression'
	22	'Mental health problem'
	23	'Gestational diabetes mellitus'
	24	'GDM'
	25	'Hypertensive disorder of pregnancy'
	26	'HDP'

	27	'preeclampsia'
	28	'Maternal body weight'
	29	'Excess weight gain'
Pregnancy outcomes	30	'Abnormal fetal growth'
	31	'Intrauterine growth restriction'
	32	'Low birth weight'
	33	'LBW'
	34	'IUGR'
	35	stillbirth
	36	'Small of gestational age'
	37	'Preterm birth'
	38	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37
	39	#15 AND #38

Supplementary Table S2: Quality assessment tools

Study Quality Evaluation		
Item	**Question**	**Coding**
1. Question	Was the research question or objective in this paper clearly stated?	0-No 1-Yes
2. Population	Was the study population clearly specified and defined?	0-No 1-Yes
3. Participation	Was the participation rate of eligible persons at least 50%?	0-No 1-Yes
4. Inclusion/Exclusion Criteria	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	0-No 1-Yes
5. Sample Size	Was a sample size justification, power description, or variance and effect estimates provided?	0-No 1-Yes
6.	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	0-No 1-Yes
7. Timeframe	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	0-No 1-Yes
8. Levels of Exposure	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	0-No 1-Yes
9. Independent Variable	Were the exposure measures (independent variables) clearly defined, valid, reliable, and	0-No 1-Yes

	implemented consistently across all study participants?	
10. Longitudinal/Repeated ACEs	Was the exposure(s) assessed more than once over time?	0-No 1-Yes
11. Dependent Variable	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	0-No 1-Yes
12. Objectivity independent variable	Does the study use objective reports or multiple-methods to measure maternal ACEs? Objective measure = child abuse reports Multiple methods = self-report and corroborated reports.	0-self report 1-objective measure/multiple methods
13. Objective dependent variables	Does the study use different reporters or multiple-methods to measure maternal health/mental health outcomes? Objective measure = hospital report, diagnosis by physician, measurement by health care professional	0-self report 1-objective measure/multiple methods
14. Lost to Follow-Up	Was loss to follow-up after baseline 20% or less?	0-No 1-Yes
15. Confounder	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	0-No 1-Yes
Total	A sum of all items was calculated to obtain a total quality score (0-15).	

Supplementary Table S3: Quality of the study

SI#	First Author/Pub Date	Question	Population	Participation	Inclusion/Exclusion Criteria	Sample Size	Exposures	Timeframe	Levels of Exposure	Independent Variable	Longitudinal/Repeated ACEs	Dependent Variable	Objectivity independent variable	Objective dependent variables	Lost to Follow-Up	Confounder	Overall	Quality score
1	Christiaens/2015	1	1	0	1	1	1	1	1	1	0	0	1	0	0	1	10	Moderate
2	Grimstad/ 1999	1	1	1	1	1	1	1	0	0	0	0	1	1	0	0	9	Low
3	Hardcastle et al., 2022	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14	High
4	Noll/ 2007	1	1	1	0	0	1	1	0	0	0	0	1	1	0	0	7	Low
5	Leeners/ 2014	0	1	1	0	0	1	0	0	0	0	0	0	0	0	1	10	Moderate
6	Selk/2016	1	**1**	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
7	Harville/2010	1	1	1	0	1	1	1	1	1	1	1	0	1	0	1	12	Moderate
8	Versteegen et al., 2021	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14	High
9	Stanhope et al., 2020	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14	High
10	Schoenaker et al., 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14	High
11	Miller et al., 2017	1	1	1	1	1	1	0	0	1	0	1	0	1	0	0	9	Low
12	Mersky et al., 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
13	Mason et al., 2016	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
14	Cammack et al., 2018	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
15	BALA et al., 2020	1	1	1	1	1	1	1	0	1	0	1	1	1	0	1	12	Moderate
16	Ben Salah et al, 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
17	Bhengu, 2019	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	12	Moderate
18	Gillespie et al. (2017)	1	1	1	0	1	1	1	0	1	1	1	1	0	0	0	10	Moderate
19	Leeners et al, 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15	High
20	McDonnell and Val et al, 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	14	High
21	Shaikh et al., 2019	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	11	Moderate
22	Smith et al., 2016	1	1	1	1	0	0	1	1	1	0	1	0	0	1	1	10	Moderate
23	Ranchod et al, 2016	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	8	Low
24	Appleton et al, 2019	1	1	1	1	0	0	1	0	1	0	1	0	1	1	0	9	Low
25	Fredriksen et al, 2017	1	1	1	1	0	0	1	1	1	0	1	0	0	0	0	8	Low

26	Hantsoo et al,2019	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	8	Low
27	Letourneau et al, 2019	1	1	1	1	0	0	1	1	1	0	1	0	0	1	1	10	Moderate
28	Howell1,2020	1	1	1	1	0	1	1	1	1	1	1	0	0	1	1	12	Moderate
29	Narayan et al, 2018	1	1	1	1	0	0	1	1	1	0	1	0	0	1	0	9	Low
30	Racine et al, 2020	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	8	Low
31	Young-Wolff et al, 2019	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	11	Moderate
32	Barrios et al, 2015	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	11	Moderate

Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-14
		(b) Give reasons for non-participation at each stage	8-14
		(c) Consider use of a flow diagram	8-14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-14
		(b) Indicate number of participants with missing data for each variable of interest	8-14
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-14
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8-14
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8-14
		Cross-sectional study—Report numbers of outcome events or summary measures	8-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-14
		(*b*) Report category boundaries when continuous variables were categorized	8-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

BMJ Open

Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-063826.R2
Article Type:	Original research
Date Submitted by the Author:	24-Apr-2023
Complete List of Authors:	Mamun, Abdullah; The University of Queensland Biswas, Tuhin; University of Queensland, Scott, James; University of Queensland Sly, P.D.; University of Queensland, Queensland Childrens Medical Research Instit McIntyre, David; Mater Research Institute The University of Queensland Thorpe , Karen ; University of Queensland Boyle , Frances; University of Queensland Dekker, N; University of Queensland, Centre for Clinical Research Doi, Suhail; Qatar University, Population Medicine Mitchell, Murray; QUT, Faculty of Health, School of Biomedical Sciences McNeil, Keith; Queensland Health Kothari, Alka ; University of Queensland Hardiman, Leah; Queensland Health Callaway, Leonie Kaye; Queensland Health
Primary Subject Heading:	Global health
Secondary Subject Heading:	Public health, Mental health, Health policy
Keywords:	Epidemiology < TROPICAL MEDICINE, EPIDEMIOLOGY, Adverse events < THERAPEUTICS, Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, Prenatal diagnosis < OBSTETRICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Author's names: Abdullah Al Mamun, PhD[1,2], Tuhin Biswas, PhD[1,2]; James G. Scott, PhD[3,4,5]; Peter D Sly, MD, DSc[6];David McIntyre,PhD[7]; Karen Thorpe,PhD[1,2];Frances M. Boyle,PhD[1];Marloes Dekker Nitert PhD[8], Suhail A. R. Doi, PhD[9,10];Murray Mitchell, PhD[11]; Keith McNeil, PhD[12]; Alka Kothari, MD FRANZCOG[13,14], Leah Hardiman MSC[15], Leonie Callaway, PhD[15]

Author affiliations:

1. UQ Poche Centre for Indigenous Health, The University of Queensland, Queensland, Australia.
2. ARC Centre of Excellence for Children and Families over the Life Course, The University of Queensland, QLD, Australia
3. Mental Health Research Program, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia
4. Metro North Mental Health, Royal Brisbane and Women's Hospital, Herston, QLD, Australia
5. Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, QLD, Australia
6. Children's Health and Environment Program, Child Health Research Centre, The University of Queensland, QLD, Australia

7. Mater Research, Faculty of Medicine, University of Queensland, Mater Health, QLD, Australia.
8. School of Chemistry and Molecular Biosciences, The University of Queensland, QLD, Australia
9. Research School of Population Health, Australian National University, Canberra, Australian Capital Territory
10. Department of Population Medicine, College of Medicine, Qatar University, Doha
11. Faculty of Health, School of Biomedical Sciences, The Queensland University of Technology, QLD, Australia
12. Prevention Division, Queensland Health, QLD, Australia
13. Department of Obstetrics & Gynaecology, Redcliffe Hospital, Anzac Avenue, Redcliffe, QLD, Australia
14. Faculty of Medicine, The University of Queensland, QLD, Australia
15. Women's and Children's Stream - Metro North Hospital and Health Services, QLD, Australia
16. Institute for Social Science Research, The University of Queensland, QLD, Australia
17. Asian University for Women (AUW), Chittagong, Bangladesh
18.

Corresponding author:

Abdullah Al Mamun

UQ Poche Centre for Indigenous Health, The University of Queensland, Queensland, Australia.

74 High Street, Queensland 4068, Australia·

Email: mamun@sph.uq.edu.au

Telephone: +61 7 336 53163

Abstract

Background:

Adverse childhood experiences (ACEs) have a profound negative impact on health. However, the strength of the association between ACEs and pregnancy complications and adverse pregnancy outcomes is not well quantified or understood.

Objectives:

Conduct a systematic review and meta-analysis of the association between ACEs and risk of pregnancy complications and adverse pregnancy outcomes.

Search Strategy:

A comprehensive search was conducted using PubMed, EMBASE, CINAHL, PsycINFO, ClinicalTrials.gov and Google scholar up to July 2022.

Data Collection and Analysis:

Two reviewers independently conducted the screening and quality appraisal using a validated tool. Meta-analysis using the quality-effects model on the reported odds ratio (OR) was conducted. Heterogeneity and inconsistency were examined using the I^2 statistics.

Results:

Thirty-two studies from 1,508met a priori inclusion criteria for systematic review, with twenty-one included in the meta-analysis. Pooled analyses showed that exposure to ACEs increased

the risk of pregnancy complications (odds ratio, OR=1·37, 95% CI: 1·20-1.50) and adverse pregnancy outcomes (OR=1·31, 95% CI: 1·16-1·48). In sub-group analysis, maternal ACEs were associated with gestational diabetes mellitus(OR=1·39, 95% CI: 1.11-1·74),antenatal depression (OR=1·59, 95% CI: 1·15-2·20), low offspring birth weight (OR=1·27, 95% CI: 1·02-1·59), and preterm delivery (OR=1·41, 95% CI: 1·16-1·71).

Conclusion:

The results suggest that exposure to ACEs increase the risk of pregnancy complications and adverse pregnancy outcomes. Preventive strategies, screening and trauma-informed care need to be examined to improve maternal and child health.

Funding statement: This research was partially supported by the Australian Research Council Centre of Excellence for Children and Families over the Life Course (CE200100025).

Keywords: Adverse childhood experiences, pregnancy complications, adverse pregnancy outcomes

Tweetable abstract:

Adverse childhood experiences linked to pregnancy complications and adverse pregnancy outcomes.

Strengths and limitations of this study

- Maternal ACEs were associated with an increased risk of pregnancy complications, including GDM, GWG, HDP and depression/anxiety during pregnancy.
- ACE exposure showed a significant association with any adverse pregnancy outcome.
- Most of the included studies are from high-income western countries. Due to the lack of data, we could not conduct the ACEs item-specific analysis.
- The dose-response relationship in all studies could not be assessed as different studies use different screening tools and cut-off values.

Introduction

Adverse Childhood Experiences (ACEs)[1]are psychosocial stressors and traumas experienced by an individual before 18 years of age[2, 3]The pioneering study by Fellitti and colleagues (1998) demonstrated that exposure to ACEs is common, ACEs co-occur and that exposure to multiple ACEs are associated with an increased risk of health risk behaviours and illnesses.[4]Subsequently, a growing body of research has continued to provide consistent evidence that ACEs are a major public health issue due to their high prevalence and harmful effects that ACEs have on human health throughout life.[5, 6]

Early life experiences are recognized as essential determinants for health outcomes later in life especially in pregnant women and their children.[7]Adverse health outcomes in pregnancy can then result in intergenerational transmission of adverse health outcomes. Perhaps this occurs because women who have experienced ACEs may be a vulnerable group for development of health risk behaviours, including smoking, drug and alcohol use and sedentary lifestyle, along with consequences of trauma such as poor sleep.[5] These behaviours increase the risk of pregnancy complications including gestational diabetes mellitus (GDM), hypertensive disorder of pregnancy (HDP),excess gestational weight gain (GWG), depression/anxiety during

pregnancy[8] and adverse pregnancy outcomes including low birth weight and preterm birth.[9-11]Systematic reviews have reported women who had experienced child maltreatment are more likely to have pregnancy complications and that physical abuse and household substance abuse were associated with greater risk of GDM[12, 13] resulting in intergenerational transmission of adverse health outcomes. Overall, those reporting exposure to multiple ACEs (mostly 4 or more) have an increased risk of physical, mental, and substance use disorders.[14]

There is little information about ACEs and the associated risk of pregnancy complications and adverse birth outcomes. A longitudinal study in Australia reported that women exposed to three or more ACEs had an elevated GDM risk.[15] In contrast, a longitudinal study from the USA reported no significant association between ACEs (for each score change and reported 4 or more ACEs) and GDM.[16]A systematic review suggests that total ACEs (score in continuous scale) are associated with preterm birth, although this finding needs to be confirmed in other studies to explore the associations between ACEs and preterm birth using appropriate and valid instruments.[17] Another systematic review and meta-analysis reported that maternal history of abuse before pregnancy was significantly associated with preterm delivery and low birth weight.[18] No systematic review and meta-analysis has investigated the association of ACEs and the risk of pregnancy complications including GDM, HDP, GWG, depression/anxiety during pregnancy and adverse pregnancy outcomes. This study aims to systematically review and meta-analyse existing studies to establish the extent of association between ACEs and pregnancy complications and adverse birth outcomes. Understanding these associations will inform maternal clinical care and support for offspring of those women exposed to ACEs.

Methods

In this systematic review and meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [19] and the Meta-Analysis of Observational Studies in Epidemiology protocol [20] to ensure all necessary steps were followed. In accordance with the guidelines, the systematic review and meta-analysis protocol was registered in PROSPERO (CRD42021278030).

Literature search strategy

Our search included studies published to July 2022using PubMed, EMBASE, CINAHL, PsycINFO, ClinicalTrials.gov and Google scholar. The search strategy employed with PubMed is: ((((((((((("adverse childhood experiences") OR ("childhood adversities")) OR ("childhood abuse")) OR ("childhood maltreatment")) OR ("child trauma")) OR ("adverse childhood events")) OR ("childhood sexual abuse")) OR ("childhood physical abuse")) OR ("childhood mental abuse")) OR ("childhood trauma")) OR ("childhood violence")) OR ("childhood hardship")) OR ("childhood suffering")) OR ("childhood Stress")) AND ((((((((((((("pregnancy complications") OR ("Depression")) OR ("Anxiety")) OR ("Prenatal depression")) OR ("Depressive symptoms")) OR ("Antenatal depression")) OR ("Mental health problem")) OR ("gestational diabetes mellitus")) OR ("GDM")) OR ("hypertensive disorder of pregnancy")) OR ("HDP")) OR ("preeclampsia")) OR ("maternal body weight")) OR ("excess weight gain")) OR ("abnormal fetalgrowth")) OR ("Intrauterine growth restriction")) OR ("Low birth weight")) OR (LBW))OR (IUGR)) OR (Stillbirth)) OR ("small of gestational age")) OR ("preterm birth")). This search details are presented in a supplementary table (Table S1).

Inclusion criteria

Studies were included if the full-text was published in English, population was pregnant women, reported any ACEs including childhood maltreatment (childhood physical, emotional and sexual abuse, childhood physical and emotional neglect and exposure to parental intimate partner violence), childhood trauma or childhood hardship/suffering and if studies reported any pregnancy-related complications according to National Institute of Health (NIH)[21] (GDM, HDP, GWG, depression/anxiety during pregnancy) and adverse birth outcomes such as low birth weight, intra-uterine growth restriction (IUGR), preterm birth, stillbirth. Studies were excluded if: (1) published in languages other than English; (2) included general population (not pregnant); (3) reported reviews, qualitative studies, editorials, abstracts, case reports and letters to the editor (4) explored violence during pregnancy.

Data extraction

Two independent reviewers (TB and AAM) carried out the data extraction. If AAM and TB did not reach agreement, the small group (AAM, TB, LC and JS) discussed discrepancies to reach a consensus. A similar approach was used for title/abstract and full text reviews. We excluded study protocol, systematic review, and qualitative study during the title screening phase. During the abstract screening phase, we excluded articles that didn't present any association between ACEs and pregnancy complications and outcomes (Figure-1). Relevant data from each of the selected studies was extracted including first author; study title; country of study; sample size; study design; types of ACEs; measurement scale; and outcomes (both risk of pregnancy complications and adverse pregnancy outcomes) and recorded on an Excel spreadsheet.

Quality assessment

Fifteen-point scale quality assessment tools were used to assess the quality and risk of bias of the studies. We adapted a quality assessment tool from NIH "Quality Assessment Tool for Observational Cohort and Cross-sectional studies".[22] This tool allowed assessment of the question, population, participation, inclusion/exclusion criteria, sample size, exposures, timeframe, levels of exposure, independent variables, longitudinal/repeated ACEs, dependent variable, objectively measured independent variables, objectively measured dependent variables, lost to follow-up and confounders(**Supplementary** Table S2).Overall quality score was considered as a continuous variable for bias adjustment in the pooled estimates. However, we have also categorised the overall quality score into three groups: 13-15 as high;10-12 as moderate and <10 as low.

The results of the quality assessment are presented in **Supplementary** Table S3.

Data Analysis

Meta-analysis conducted in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines. Analyses focused on the overall association between ACEs and risk of pregnancy complications and adverse birth outcomes. Subgroup data synthesis was performed only when three or more studies were available with the estimates for a similar type of ACE exposures. ACE scores were considered on the continuous scale (for each unit change) and three categories: I) none versus one ACEs; ii)two to three ACEs (low ACEs); and (iii)four or more ACEs (high ACEs).Although most of the studies reported the odds ratio (OR) as the measurement of association between exposures and outcomes, two studies reported relative risk (RR) and one hazard ratio (HR). We converted all measures of associations into ORs using conversion methods reported elsewhere.[23] In the meta-analysis, we used the quality effects model (QE)[24] for bias adjustment. The advantage of the QE model is that the between-study variability is adjusted based on the relative quality rank of the studies instead of on random variables assigned by the random effect (RE) model. The heterogeneity of the studies was reported by the I-squared value (I2) that measures the proportion of total variance between studies beyond random error.[24]We checked for publication bias through visualization by funnel plot and Doi plot.[25]All the analyses were conducted using the MetaXL software version 5.3.[26]

Patient and Public Involvement: None.

Results

The literature search resulted in 1,508 records, which were screened for duplication (n=398), review of titles (n=1,086) and further abstract evaluation (n=485). Finally, 32studies met our inclusion criteria for systematic review, and 21 were included in meta-analysis **(Figure 1)**. 75% of the studies were cohort studies and the remainder were either cross sectional or case-control studies. The majority of the studies were conducted in the USA (n = 19), with fewer studies from Canada (n=3), Europe (n=6) and other regions (n=5). The study sample sizes varied from 48 to 11,556. The publication year ranged from 1994 to 2022. Thirteen studies used the 10-item ACEs questionnaire[8, 16, 27-37], three used World Health Organization(WHO) ACE-IQ questionnaires[38-40] with one study used 8-items [41] and two studies used 19-items questionnaire[42, 43] and fourteen studies used other measures[35, 44-55] **(Table-1)**.

232 **Table-1: Characteristics of studies included in the systematic review and meta-analysis**

SI#	First Author/Pub Date	Country	Study design	Sample size	Measurement scale
1	Christiaens/2015	Canada	Case-control	622	10-item self-report tool by Felliti et al
2	Grimstad/ 1999	Norway	Case-control	174	Were asked about the character of the experience(s): Genital Touch; Forced to touch the other person's genitals; Attempted Coitus; 4. Penile Vaginal Coitus
3	Noll/ 2007	USA	Cohort	186	Childhood sexual abuse
4	Leeners/ 2014	Switzerland	Cohort	255	Childhood sexual abuse experiences were additionally explored using questions modified by Wyatt
5	Selk/2016	USA	Case-control	51434	The measure of physical abuse included items from the Revised Conflict Tactics Scale (CTS); The sexual abuse measure was derived from the survey by Finkelhor et al
6	Harville/2010	UK	Cohort	4865	The phrase "childhood hardship" is used herein to refer to a num-ber of adverse situations in childhood: • Financial/structural hardship • No interest in education • Family dysfunction • Lack of supportive caregiving • Violence/mental health issues • Issues of family structure • No. of hardships
7	Appleton et al, 2019	USA	Cohort study	126	10-item self-report tool by Felliti et al
8	Versteegen et al., 2021	USA	Cohort	30	10-item self-report tool by Felliti et al
9	Stanhope et al., 2020	USA	Cohort	2319	10-item self-report tool by Felliti et al
10	Schoenaker et al., 2019	Australia	Cohort	11,556	10-item self-report tool by Felliti et al
11	Miller et al., 2017	USA	Prospective study	744	asked women a series of questions about their family's conditions during childhood
12	Mersky et al., 2019	USA	Longitudinal	1848	19-item assessment that has demonstrated good internal consistency
13	Mason et al., 2016	USA	Cohort	45,550	Physical abuse and Sexual abuse

14	Cammack et al., 2018	USA	Cohort	230	Childhood Trauma Questionnaire Short-Form (CTQ)
15	BALA et al., 2020	Rhode Island	Population-based survey	3350	7-item questionnaire
16	Ben Salah et al, 2019	Tunesia	Prospective follow-up study	593	ACE-International Questionnaire (ACE-IQ)
17	Bhengu, 2019	South Africa	cross-sectional	223	WHO-ACE IQ
18	Gillespie et al. (2017)	USA	Prospective observational design	89	The Stress and Adversity Inventory (STRAIN)
19	Leeners et al, 2014	Switzerland	cohort	225	using questions modified from a questionnaire developed by Wyatt
20	McDonnell et al, 2014	USA	Cohort	398	10-item self-report tool by Felliti et al
21	Shaikh et al., 2019	Pakistan	Cohort	300	World Health Organization 31-item ACEs –
22	Smith et al., 2016	USA	Cohort	2303	The main modification of the instrument was to collapse the sexual events before the age of 18 questions into 1 question asking about childhood sexual abuse prior to age 18.
23	Ranchod et al, 2016	USA	Longitudinal study	2,873	4-Item questionnaire
24	Fredriksen et al, 2017	Norway	Cohort	762	10-item self-report tool by Felliti et al
25	Hantsoo et al,2019	USA	Observational study	48	10-item self-report tool by Felliti et al
26	Howell1,2019	USA	Observational study	101	10-item self-report tool by Felliti et al
27	Letourneau et al, 2019	Canada	Cohort	907	10-item self-report tool by Felliti et al
28	Narayan et al, 2018	USA	Cohort	101	10-item self-report tool by Felliti et al
29	Racine et al, 2020	Canada	Cohort	1994	10-item self-report tool by Felliti et al
30	Young-Wolff et al, 2019	USA	Cohort	355	10-item self-report tool by Felliti et al
31	Barrios et al, 2015	USA	Cohort	1,521	Eight questions from CDC
32	Hardcastle et al., 2022	UK	Cross sectional	865	10-item self-report tool by Felliti et al

In total, 32 studies were included for quality assessment. Eleven studies (34.38%) were assessed as high quality, 12 studies (37.50%) were assessed as moderate quality, and 9 studies (28.13%) were assessed as poor quality(Table S3).ACEs and risk of pregnancy complications

ACEs and GDM: Six studies[8, 16, 35, 36, 51, 56] described an association between ACEs and GDM and only one study reported (**Table-2.1)**. there was no association between ACEs and GDM[42]. A large epidemiological study in Australia [56] reported that, in pregnant women, exposure to any three ACEs (adjusted relative risk, aRR=1.73, 95% CI:1·0, 3·0) or four or more ACEs (aRR=1·70, 95% CI:1·00, 2·90) was associated with elevated GDM risk after adjusting preconception BMI, unhealthy diet, parity, and maternal age. Another study in the USA by Mason et al., 2016[35] reported that both moderate (adjusted odds ratio, aOR=1·08, 95% CI:0.96, 1·22) and severe(aOR=1.42, 95% CI:1·21, 1·66)childhood physical abuse was associated with an increased risk of GDM. This study also reported that forced sexual activity during childhood was associated with an increased risk of GDM (aOR1·30, 95% CI:1·14, 1·49).

ACEs, GWG and HDP: Only one study by Ranchod et al., 2016[54]examined the association between ACEs and GWG. They found that exposure to physical abuse and household alcohol abuse were independently associated with a 20% increase in the risk of excessive GWG. A study by Stanhope et al., 2020[8] found that for each ACEs score, there was a slight increase in the HDP risk (aOR=1·03, 95% CI:0·71, 1·49), although it was not statistically significant. However, they found that physical abuse (aOR= 1·22, 95% CI: 1·10-1·42) and household alcohol abuse (aOR= 1·21, 95% CI: 1·11-1·32) were associated with a significant increase in the risk of excessive GWG (**Table-2.1)**.

Table-2.1: Summary of published measures of effect.

1	Appleton et al, 2019	Depression	ACE's score (continuous)	Pearson's correlations coefficients (0.37)
2	Versteegen et al., 2021	GDM	ACEs total	1.05 (0.98, 1.14)
			ACEs binary	2.85 (1.15-7.06)
3	Stanhope et al., 2020	GDM	ACEs 4+	1.03 (0.71, 1.49)
			Continuous ACE score	0.96 (0.88, 1.04)
		HDP	ACEs 4+	1.03 (0.71, 1.49)
			Continuous ACE score:	1.03 (0.71, 1.49)
4	Schoenaker et al., 2019	GDM	Three ACEs	1.73, (1.02, 3.01)
			Four or more ACEs	1.76, (1.04, 2.99)
5	Mason et al., 2016	GDM	Mild physical abuse	1.08 (0.96, 1.22)
			Moderate physical abuse	11.16 (1.04, 1.29)
			Severe physical abuse	1.42 (1.21, 1.66).
			Forced sexual activity	1.30 (1.14, 1.49)
			Combine	1.42, (1.21, 1.66)
6	BALA et al., 2020	GDM	3 or more ACEs	1.24, (0.81–1.90)
			1–2 ACEs	1.18, (0.90– 1.55)
7	McDonnell et al, 2014	GDM		GDM not correlated with ACE indicators
8	Ranchod et al, 2016	GWG	Physical abuse	1.2, (1.1-1.4)
			Household alcohol abuse	1.2, (1.1-1.3)
			Household mental illness	1.1, (0.9-1.2).
9	Fredriksen et al., 2017	Depression	ACEs continuous	1.3, (0.92-1.82)
10	Hantsoo et al.,2019	Depression	< 2 ACES	EPDS (Median [IQR]): 5 [3, 6]
			2 or more ACES	EPDS (Median [IQR]): 3 [1.5, 6.0]
11	Howell et al., 2020	Depression	ACEs continuous	Adverse childhood experiences had a direct effect on depression, B=1.11, standard error=.44, p=.01,
12	Letourneau et al, 2019	Depression	ACEs continuous	Maternal ACEs were associated with symptoms of anxiety and depression during pregnancy
13	Narayan et al et al., 2018	Depression	ACEs continuous	Maternal ACEs were associated with depression during pregnancy ($\beta = 0.32$, $p < 0.01$).
14	Racine et al et al., 2020	Depression	ACEs continuous	1.26, (1.12-1.43)
15	Young-Wolff et al et al., 2019	Depression	3+ ACEs	3.08, (1.12-7.39)
			1–2 ACEs	2.42 (1.09–5.41)
16	Barrios et al., 2015	Depression		Depression: OR: 2.07; 95% CI: 1.58-2.71

ACEs and depression/anxiety: Nine studies[27-33, 37, 41] examined the association between ACEs and depression/anxiety with almost all studies reporting a significant positive association during pregnancy (**Table-2.1)**. For example, a large cohort study in Canada by Racine et al, 2020[32] reported that ACEs were associated with depressive symptoms in pregnancy (aOR =1·26, 95% CI :1·12–1·43). Another study by Letourneau et al, 2019[30] reported that for each maternal ACE, there was an increased risk of symptoms of anxiety and depression during pregnancy. An observational study in the USA by Hantsoo et al[28, 29] reported that ACEs directly affected depression (B=1·1, standard error=·44, p=·01).

Meta-analytic results for maternal ACEs and risk of pregnancy complications:

A total of 11 studies (72,889 participants) were available for the quality-effect meta-analysis, which produced an association between maternal any ACEs and risk of any adverse pregnancy complications (OR=1·37, 95% CI: 1·20-1·57)**(Figure-2)**. In risk factor-specific sub-analysis, five studies (7116 participants)were available for meta-analysis, which produced a moderate association between maternal ACEs and risk of GDM (OR=1·39, 95% CI: 1.11-1·74). For depression/anxiety during pregnancy, four studies (6116 participants) were available for this meta-analysis, which produced an association between maternal ACEs and risk of depression/anxiety during pregnancy (OR=1·5, 95% CI: 1·15-2·2).Both low (OR=1·30, 95% CI: 1·10-1·50) and high (OR=1·41, 95% CI: 1·02-1·90) number of ACEswere associated with and pregnancy complications (**Supplementary** Figure S1**.1 and 1.2**).

ACEs and adverse pregnancy outcomes

ACEs and preterm birth: Out of 31 studies, 12 [34, 38, 40, 42-48, 50, 55, 57] reported the association between ACEs and preterm birth(**Table-2.2)**. A study in Tunisia by Ben Salah et al. (2019) reported that after adjustment for high-risk pregnancies, environmental tobacco smoke, and intra-familial ACEs, the risk of premature birth was significantly associated with exposure to collective violence (P-value< 0.001) and witnessing community violence (P-value< 0·05). In another study, Harville et al[48] reported that violence exposure during childhood was associated with a 44% increased risk of preterm birth (adjusted RR= 1·40; 95% CI: 1·00-1·90). They also found the family mental health issues increased by 24%, and a 25% increase in the risk of preterm birth. A case-control study in the USA by Selk et al[47] reported that women exposed to forced sex during childhood had a 22% greater risk of preterm birth (adjusted RR=1·2, 95% CI: 1·10-1·30) than those in the no exposure group. Furthermore, exposure to physical and sexual abuse during childhood was associated with a 35% greater risk of preterm birth (adjusted RR=1·30, 95% CI: 1·10-1·60). A study by Miller et al., reported that mothers' childhood economic hardship was independently associated with multiple adverse birth outcomes.[49]A study by Gillespie et al reported that maternal childhood abuse was associated with birth timing (birth timing was operationalized as a days gestation at birth continuous variable and calculated according to obstetric estimate of date of delivery and actual date of delivery extracted from the prenatal and labor and delivery records).[52]

ACEs and low birth weight:

Out of 31 studies, six [38, 42, 44, 48, 50, 53] reported an association between ACEs and low birth weight (**Table-2.2)**.

304 **Table-2.2: Summary of published measures of effect.**

SI#	First Author/Pub Date	Outcomes	Types of ACEs and analytical unit	Findings (OR, 95% CI)
1	Christiaens et al., 2015	Preterm birth	High ACE score (≥2 ACE)	2.09, (1.10–3.98)
			ACE's score (continuous)	1.18, (0.99–1.40)
2	Grimstad et al.,1999	Preterm birth	Sexual Abuse	1.03, (0.44-2.4)
		Low birth weight	Sexual Abuse	1.21, (0.5-2.93)
3	Noll et al., 2007	Preterm birth	Sexual abuse	2.16, (0.77-6.06)
4	Leeners et al., 2014	Preterm birth	Sexual abuse	2.47, (1.11-5.51)
5	Selk et al., 2016	Preterm birth	Severe physical only	1.02, (0.88- .17)
			Forced sex only	1.22, (1.1-1.35)
			Experienced both severe abuse types	1.35, (1.13-1.62)
6	Harville et al., 2010	Preterm birth	Financial/structural hardship	1.20 (0.90-1.60)
			No interest in education	1.17 (0.93-1.48)
			Family dysfunction	1.20 (0.94-1.52)
			Lack of supportive caregiving	0.98 (0.81-1.19)
			Violence/mental health issues	1.24 (0.94-1.63)
			Issues of family structure	1.25 (1.02-1.54)
			No. of hardships (≥ 4)	1.45 (1.09-1.93)
		Low birth weight	Financial/structural hardship	1.18 (0.88-1.60)
			No interest in education:	1.18 (0.88-1.60)
			Family dysfunction	1.18 (0.88-1.60)
			Lack of supportive caregiving	1.18 (0.88-1.60)
			Violence/mental health issues	1.48 (1.12-1.96)
			Issues of family structure	1.48 (1.12-1.96)
			No. of hardships (≥ 4)	1.48 (1.12-1.96)
11	Miller et al., 2017	Birth outcomes	Childhood economic hardship	Mother's hardship independently associated with multiple adverse birth outcomes
12	Mersky et al., 2019	Preterm birth	ACE scores (continuous)	1.07, (1.01–1.12)
			1 or 2 ACEs	1.22 (0.79–1.89)
			3 or 4 ACEs	1.29 (0.82–2.02)
			5 or more ACEs	1.46 (0.95–2.26)
		Low birthweight	ACE scores (continuous)	1.08, (1.03–1.15)
			1 or 2 ACEs	0.98 (0.62–1.56)
			3 or 4 ACEs	1.22 (0.76–1.96)
			5 or more ACEs	1.39 (0.88–2.19)
		Pregnancy loss	ACE scores (continuous)	1.12, (1.08–1.17)
			1 or 2 ACEs	0.93 (0.66–1.31)
			3 or 4 ACEs	1.27 (0.89–1.80)
			5 or more ACEs	1.27 (0.89–1.80)
14	Cammack et al., 2018	Low Birth Weight	Emotional Abuse	0.88 (0.66–1.00) Cohen's Kappas (95% CI)
			Physical Abuse	0.50 (0.01–0.99)
			Sexual Abuse	0.75 (0.43–1.00)
			Emotional Neglect	0.59 (0.18–1.00)
			Physical Neglect	0.28 (−0.16–0.73)

		Preterm Birth	Emotional Abuse	0.78 (0.55–1.00)
			Physical Abuse	0.69 (0.36–1.00)
			Sexual Abuse	0.78 (0.55–1.00)
			Emotional Neglect	0.44 (0.12–0.77)
			Physical Neglect	0.39 (−0.03–0.81)
		NICU Admission	Emotional Abuse	0.58 (0.25–0.91)
			Physical Abuse	0.28 (−0.15–0.71)
			Sexual Abuse	0.73 (0.45–1.00)
			Emotional Neglect	0.55 (0.20–0.90)
			Physical Neglect	0.55 (0.20–0.90)
16	Ben Salah et al, 2019	Preterm Birth Low birth weight	ACEs continuous	After adjustment for high-risk pregnancies, environmental tobacco smoke, and intra-familial ACEs, the risk of premature birth was significantly associated with exposure to collective violence (P < 0.001) and witnessing community violence (P < 0.05).
17	Bhengu et al., 2019	Preterm Birth	ACEs continuous	1.21, (1.03-1.43)
18	Gillespie et al. (2017)	Birth timing	ACEs continuous	Cumulative childhood stress predicted birth timing (p = 0.01).
19	Leeners et al, 2014	Preterm Birth		CSA, physical abuse as well as other ACE were associated with an increased risk for premature delivery
21	Shaikh et al., 2019	Preterm Birth	ACEs continuous	We found no association between ACE and preterm birth
22	Smith et al., 2016	Birth weight and shorter gestational age	ACEs continuous	Each additional ACE decreased birth weight by 16.33 g and decreased gestational age by 0.063.
32	Hardcastle et al., 2022	Preterm Birth	1 ACE	0.80 (0.32-2.00)
			2–3 ACEs	1.17 (0.46-2.97)
			≥4 ACEs	2.67 (1.14-6.23)

Harville et al reported that violence exposure during childhood was associated with an increased risk of low birth weight(adjusted OR= 1·5; 95% CI: 1·1-2·0). They also found that violence/mental health issues (adjusted OR=1·4, 95% CI:1·1-1·9) and issues of family structure increased the risk of low birth weight (adjusted OR=1·4, 95% CI:1·1-1·9). A study by Smith et al. reported that each additional ACE decreased gestational age at birth as well as birth weight.[53]

Meta-analytic results for maternal ACEs and adverse pregnancy outcomes:

A total of 12studies were available for this quality-effects meta-analysis, which produced an association between maternal ACEs and any adverse pregnancy outcomes (OR=1·31, 95% CI: 1·17-1·47). In a sub-analysis of eight studies (59,607participants), the quality-effects meta-analysis showed an association between maternal ACEs and preterm birth (OR=1·41, 95% CI: 1·16-1·71). On the other hand, three studies (7,014 participants) were available for the quality-effects meta-analysis for low birth weight, which showed an association between maternal ACEs and low birth weight (OR=1·27, 95% CI: 1·17-1·47) **(Figure-3)**. In low (one to three ACEs) and high (four+) ACEs specific analysis, five studies reported low ACEs exposure and nine studies reported high ACEs exposure. Both low (OR=1·27, 95% CI: 1·05-1·54) and high (OR=1·41, 95% CI: 1·20-1·65) ACE exposure showed a significant association with any adverse pregnancy outcome. For each additional unit increase in the number of ACEs, the odds of adverse pregnancy outcomes increased 1.10 times **(**OR=1·10, 95% CI: 1·05-1·15) (**Supplementary figure** S2.1 and 2.2).

Discussion

This systematic review and meta-analysis found that maternal ACEs were associated with an increased risk of pregnancy complications including GDM, HDP, GWG and mental health

during pregnancy. Similarly, this study also found that maternal ACEs were associated with an increased risk of adverse pregnancy outcomes including preterm birth and low birth weight. All these associations were stronger for 4 or more compared to less than 4 ACEs. There was a dose-response association between ACEs and adverse pregnancy outcome. Overall, findings of this study suggest there is a robust association between ACEs and pregnancy complications and adverse pregnancy outcomes. Early prevention of ACEs might reduce the risk of pregnancy complications and adverse outcomes.

To our knowledge, this is the first systematic review and meta-analysis to assess the association between ACEs and pregnancy complications and adverse pregnancy outcomes. A recent systematic review and meta-analysis reported an association between ACEs and maternal depression and/or anxiety in the perinatal period (pregnancy to 1-year postpartum). [22]though the results of our study are not directly comparable to this study because outcomes were considered at different perinatal windows and results were presented differently (e.g., effect size vs. odds ratio). Our results on maternal ACEs and increased risk of adverse pregnancy outcomes are more comprehensive than previous systematic reviews [58][59][18] due to the availability of 12 recent primary studies. Overall, the direction and strength of the associations in our study is similar to these earlier studies [58][59][18].

There could be several potential direct and indirect pathways to explain the relationship between ACEs and pregnancy complications and adverse pregnancy outcomes. Direct mechanisms may include altering the regulation of stress-signalling pathways [60] and immune system function[61]; changing brain structure and function; and changing the expression of DNA and by accelerating cellular ageing[62].For example, abuse or neglect might directly lead to malnutrition. Similarly, stress can directly lead to dysregulation of the hypothalamic pituitary-adrenal axis and associated neuro-endocrine-immune[63] as well as epigenetic effects[64]. Results from animal models [65, 66] and longitudinal human studies such as the

Nurses' Health Study[35] have proposed that a strong history of ACEs may alter hypothalamic-pituitary-adrenal axis as reflected by elevated cortisol levels that in turn alter glucose metabolism and body weight regulation. Brain development begins in fetal life and continues into early adulthood. Early life maternal ACEs may alter the structure and function of the brain.[67, 68] These neurodevelopmental alterations may result in neuroendocrine disruption of cortisol regulation, linked to glucose metabolism [69, 70]. The experience of ACEs increased the risk of physical or sexual abuse during pregnancy and is associated with placental damage, uterine contractions, premature rupture of membranes, and genitourinary infections which ultimately increase the risk of preterm birth and low birth weight[71]. Exposure to ACEs is also associated with an increased risk of health risk behaviours including substance use, physical inactivity and unhealthy diet[4]. Previous research has shown that ACEs are associated with pre-pregnancy obesity.[72]In addition, it is also established that socioeconomic status and cumulative disadvantage produces health disparities across the life course[73]. Any of these mechanisms could explain the transgenerational nature of obesity and diabetes in families affected by maternal ACEs. Chronic inflammation, unhealthy behaviours, poor sleep and altered stress regulatory pathways are risk factors for adverse pregnancy complications, including GDM, HDP and depression/anxiety [74, 75]. The interplay of these different pathways remains largely unclear.

According to our findings and other systematic review evidence, it may be valuable to assess the role of routine ACEs screening during pregnancy to improve maternal and child health. Trauma-informed care is not well incorporated into clinical practice guidelines. Much of the emphasis in maternity care is on individual behaviour change, including advice about diet, exercise, smoking cessation and uptake of clinical care. Approaches that do not incorporate the personal experiences of trauma by women attending antenatal services may inadvertently cause

iatrogenic harm. For many years, there has been an interest in improving pregnancy outcomes by focusing on a limited set of physical parameters that can easily be measured such as gestational weight gain, without attention to the underlying mechanisms.[76, 77] Overall, studies of diet and exercise in pregnancy to reduce GDM, HDP and other adverse pregnancy outcomes have been disappointing.[78]

A recent scoping review by Tran et al.[79] found that healthcare providers perceive that they are not being trained to screen for ACEs in their undergraduate training program or in their professional training in clinical settings. In addition, healthcare workers already have a high demand on their time and limited capacity to incorporate new practices without additional resources. There is some controversy about whether screening for ACEs is a safe and ethical practice, especially if the consequences of discussing ACEs (e.g. effects on mental health) cannot be readily addressed[80, 81]. These identified barriers are similar to those reported by healthcare providers in relation to ACE screening in general clinical settings[82]. Healthcare providers may appreciate the importance of asking about ACEs to help raise issues that otherwise would be unknown and unaddressed[79]. Furthermore, Mishra et al[83] found that ACEs screening did not excessively disrupt clinic workflow. and was both acceptable for the patient and feasible for the provider. However, to determine if screening for ACEs is worthwhile, studies need to assess if trauma-informed clinical care translates to improved clinical outcomes for mother and offspring.[84]Beyond screening for ACEs, our findings emphasise the importance of preventing ACEs in children to reduce immediate impacts as well as intergenerational transmission of ACEs. As well as supporting clinicians and providing services to address ACEs, there is growing awareness of the crucial role of upstream policy- and community-level interventions to improve and support positive family and social environments and a need for wide-scale testing of the effectiveness of such interventions[85][86].

There are some limitations to the current study, which reduce the generalisability of the findings. Firstly, most of the included studies are from high-income western countries. Secondly, due to the lack of data, we could not conduct the ACEs item-specific analysis. Thirdly, the dose-response relationship in all studies could not be assessed as different studies use different screening tools and cut-off values. Only five studies exploring pregnancy complications and five studies investigating adverse pregnancy outcomes could be assessed for a dose response relationship. Lastly, as we considered various types of ACE exposures in a single review, we expected much heterogeneity in the study methodologies, populations, exposures, and outcome identification. To address these limitations,the Quality Effect model, which incorporates the heterogeneity of effects across the studies and reduces the risk-of-bias assessment was used in the meta-analysis.Nevertheless, our study has several strengths considering the comprehensive nature of the inclusion criteria, including relevant studies published up to July 2021. In addition, we assessed the methodological quality of studies using standard tools appropriate for observational cohort and cross-sectional studies.

Conclusion

In conclusion, this systematic review and meta-analysis found that exposure to ACEs increases the risk of pregnancy complications and adverse pregnancy outcomes. Identification of women exposed to ACEs and personalising their care may provide opportunities to improve maternal and child mental and physical health.

Contribution to authorship

AAM and TB contributed towards literature search, data analysis and interpretation, figures and tables, and writing of the manuscript. AAM, TB, LC, JS, PS contributed towards the drafting of the protocol, review of the study design, data collection and interpretation and provided a critical review of the manuscript. AAM and SD contributed towards data

management and analysis plan and provided oversight and interpretation of the analyses. AAM, DM, KT, FB, MN, MM, KM, AK, LH contributed towards the study design and editing. AAM and LC contributed towards the design of the manuscript, development of the protocol, and critical evaluation and interpretation of the results and critical review of the manuscript.

Disclosure of interests

All other authors declare no competing interests.

Details of ethics approval

None

Funding

This research was partially supported by the Australian Research Council Centre of Excellence for Children and Families over the Life Course (CE200100025).

Data Availability: No additional data available.

445

446

Figure-1: PRISMA diagram outlining the search strategy and selection of studies included in this review.

Figure-2: Association of any ACE exposure with risk of pregnancy complications

Figure-3: Association of any ACE exposure and adverse pregnancy outcomes

References:

1. Atzl, V.M., et al., *Adverse childhood experiences and prenatal mental health: Type of ACEs and age of maltreatment onset.* Journal of family psychology, 2019. **33**(3): p. 304.
2. Hughes, K., et al., *The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis.* The Lancet Public Health, 2017. **2**(8): p. e356-e366.
3. Wickramasinghe, Y.M., et al., *Burden of adverse childhood experiences in children attending paediatric clinics in South Western Sydney, Australia: a retrospective audit.* BMJ paediatrics open, 2019. **3**(1).
4. Felitti, V.J., et al., *Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study.* American journal of preventive medicine, 1998. **14**(4): p. 245-258.
5. Petruccelli, K., J. Davis, and T. Berman, *Adverse childhood experiences and associated health outcomes: A systematic review and meta-analysis.* Child abuse & neglect, 2019. **97**: p. 104127.
6. Schroeder, K., et al., *The association between adverse childhood experiences and childhood obesity: A systematic review.* Obesity Reviews, 2021. **22**(7): p. e13204.
7. Kuh, D., et al., *Life course epidemiology.* Journal of epidemiology and community health, 2003. **57**(10): p. 778.
8. Stanhope, K.K., et al., *Adverse childhood experiences and lifetime adverse maternal outcomes (gestational diabetes and hypertensive disorders of pregnancy) in the Hispanic Community Health Study/Study of Latinos.* Annals of Epidemiology, 2020. **50**: p. 1-6.
9. Schetter, C.D. and L. Tanner, *Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice.* Current opinion in psychiatry, 2012. **25**(2): p. 141.
10. Olsen, J.M., *Integrative review of pregnancy health risks and outcomes associated with adverse childhood experiences.* Journal of Obstetric, Gynecologic & Neonatal Nursing, 2018. **47**(6): p. 783-794.
11. Dachew, B.A., et al., *Association between hypertensive disorders of pregnancy and the development of offspring mental and behavioural problems: a systematic review and meta-analysis.* Psychiatry research, 2018. **260**: p. 458-467.
12. Montgomery, E., C. Pope, and J. Rogers, *A feminist narrative study of the maternity care experiences of women who were sexually abused in childhood.* Midwifery, 2015. **31**(1): p. 54-60.
13. Montgomery, E., C. Pope, and J. Rogers, *The re-enactment of childhood sexual abuse in maternity care: a qualitative study.* BMC pregnancy and childbirth, 2015. **15**(1): p. 1-7.
14. Lê-Scherban, F., et al., *Intergenerational associations of parent adverse childhood experiences and child health outcomes.* Pediatrics, 2018. **141**(6).
15. Schoenaker, D.A., L.K. Callaway, and G.D. Mishra, *The role of childhood adversity in the development of gestational diabetes.* American journal of preventive medicine, 2019. **57**(3): p. 302-310.
16. Versteegen, M., et al., *Maternal depression, adverse childhood experiences, and social support in relation to gestational diabetes risk: results from the Albany Infant and Mother Study (AIMS).* BMC Pregnancy and Childbirth, 2021. **21**(1): p. 1-7.
17. Sulaiman, S., et al., *Total Adverse Childhood Experiences and Preterm Birth: A Systematic Review.* Maternal and Child Health Journal, 2021: p. 1-14.
18. Nesari, M., et al., *Does a maternal history of abuse before pregnancy affect pregnancy outcomes? A systematic review with meta-analysis.* BMC pregnancy and childbirth, 2018. **18**(1): p. 1-11.
19. Shamseer, L., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.* Bmj, 2015. **349**.
20. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting.* Jama, 2000. **283**(15): p. 2008-2012.

21. https://www.nichd.nih.gov/health/topics/pregnancy.
22. Racine, N., et al., *Adverse childhood experiences and maternal anxiety and depression: a meta-analysis.* BMC psychiatry, 2021. **21**(1): p. 1-10.
23. Shor, E., D. Roelfs, and Z.M. Vang, *The "Hispanic mortality paradox" revisited: meta-analysis and meta-regression of life-course differentials in Latin American and Caribbean immigrants' mortality.* Social Science & Medicine, 2017. **186**: p. 20-33.
24. Borenstein, M., et al., *Basics of meta-analysis: I2 is not an absolute measure of heterogeneity.* Research synthesis methods, 2017. **8**(1): p. 5-18.
25. Furuya-Kanamori, L., J.J. Barendregt, and S.A.R. Doi, *A new improved graphical and quantitative method for detecting bias in meta-analysis.* International journal of evidence-based healthcare, 2018. **16**(4): p. 195-203.
26. Barendregt, J.J. and S.A. Doi, *MetaXL user guide version 5.3.* EpiGear International Pty Ltd, 2016.
27. Fredriksen, E., et al., *Patterns of pregnancy and postpartum depressive symptoms: Latent class trajectories and predictors.* Journal of Abnormal Psychology, 2017. **126**(2): p. 173.
28. Hantsoo, L., et al., *Childhood adversity impact on gut microbiota and inflammatory response to stress during pregnancy.* Brain, behavior, and immunity, 2019. **75**: p. 240-250.
29. Howell, K.H., et al., *Relational resilience as a potential mediator between adverse childhood experiences and prenatal depression.* Journal of health psychology, 2020. **25**(4): p. 545-557.
30. Letourneau, N., et al., *Intergenerational transmission of adverse childhood experiences via maternal depression and anxiety and moderation by child sex.* Journal of developmental origins of health and disease, 2019. **10**(1): p. 88-99.
31. Narayan, A.J., et al., *Positive childhood experiences predict less psychopathology and stress in pregnant women with childhood adversity: A pilot study of the benevolent childhood experiences (BCEs) scale.* Child abuse & neglect, 2018. **78**: p. 19-30.
32. Racine, N., et al., *Perinatal depression: the role of maternal adverse childhood experiences and social support.* Journal of affective disorders, 2020. **263**: p. 576-581.
33. Young-Wolff, K.C., et al., *Adverse childhood experiences and mental and behavioral health conditions during pregnancy: the role of resilience.* Journal of Women's Health, 2019. **28**(4): p. 452-461.
34. Christiaens, I., K. Hegadoren, and D.M. Olson, *Adverse childhood experiences are associated with spontaneous preterm birth: a case–control study.* BMC medicine, 2015. **13**(1): p. 1-9.
35. Mason, S.M., et al., *Abuse in Childhood or Adolescence and Gestational Diabetes: a retrospective cohort study.* American journal of preventive medicine, 2016. **50**(4): p. 436-444.
36. McDonnell, C.G. and K. Valentino, *Intergenerational effects of childhood trauma: evaluating pathways among maternal ACEs, perinatal depressive symptoms, and infant outcomes.* Child maltreatment, 2016. **21**(4): p. 317-326.
37. Appleton, A.A., et al., *Social support during pregnancy modifies the association between maternal adverse childhood experiences and infant birth size.* Maternal and child health journal, 2019. **23**(3): p. 408-415.
38. Salah, A.B., et al., *Impact of social violence and childhood adversities on pregnancy outcomes: a longitudinal study in Tunisia.* Journal of global health, 2019. **9**(2).
39. Bhengu, B.S., et al., *The role of adverse childhood experiences on perinatal substance use behaviour in KwaZulu-Natal Province, South Africa.* AIDS and Behavior, 2020. **24**(6): p. 1643-1652.
40. Shaikh, K., et al., *Ethnic disparity and exposure to supplements rather than adverse childhood experiences linked to preterm birth in Pakistani women.* Journal of affective disorders, 2020. **267**: p. 49-56.
41. Barrios, Y.V., et al., *Association of childhood physical and sexual abuse with intimate partner violence, poor general health and depressive symptoms among pregnant women.* PloS one, 2015. **10**(1): p. e0116609.

42. Mersky, J.P. and C.P. Lee, *Adverse childhood experiences and poor birth outcomes in a diverse, low-income sample.* BMC pregnancy and childbirth, 2019. **19**(1): p. 1-7.
43. Do, H.P., et al., *Intergenerational effects of violence on women's perinatal wellbeing and infant health outcomes: evidence from a birth cohort study in Central Vietnam.* BMC pregnancy and childbirth, 2021. **21**(1): p. 1-14.
44. Grimstad, H. and B. Schei, *Pregnancy and delivery for women with a history of child sexual abuse.* Child abuse & neglect, 1999. **23**(1): p. 81-90.
45. Noll, J.G., et al., *Differential pathways to preterm delivery for sexually abused and comparison women.* Journal of pediatric psychology, 2007. **32**(10): p. 1238-1248.
46. Leeners, B., et al., *Risk factors for unfavorable pregnancy outcome in women with adverse childhood experiences.* Journal of Perinatal Medicine, 2014. **42**(2): p. 171-178.
47. Selk, S.C., et al., *An observational study of type, timing, and severity of childhood maltreatment and preterm birth.* J Epidemiol Community Health, 2016. **70**(6): p. 589-595.
48. Harville, E.W., et al., *Childhood hardship, maternal smoking, and birth outcomes: a prospective cohort study.* Archives of pediatrics & adolescent medicine, 2010. **164**(6): p. 533-539.
49. Miller, G.E., et al., *Mothers' childhood hardship forecasts adverse pregnancy outcomes: role of inflammatory, lifestyle, and psychosocial pathways.* Brain, behavior, and immunity, 2017. **65**: p. 11-19.
50. Cammack, A.L., et al., *An exploratory study of whether pregnancy outcomes influence maternal self-reported history of child maltreatment.* Child abuse & neglect, 2018. **85**: p. 145-155.
51. Bala, K., et al., *The Association between Adverse Childhood Experiences and Diabetes Status during Pregnancy among Women in Rhode Island, 2016-2018.* Rhode Island Medical Journal, 2020. **103**(9): p. 52-55.
52. Gillespie, S.L., et al., *Childhood stress and birth timing among African American women: Cortisol as biological mediator.* Psychoneuroendocrinology, 2017. **84**: p. 32-41.
53. Smith, M.V., N. Gotman, and K.A. Yonkers, *Early childhood adversity and pregnancy outcomes.* Maternal and child health journal, 2016. **20**(4): p. 790-798.
54. Ranchod, Y.K., et al., *Maternal childhood adversity, prepregnancy obesity, and gestational weight gain.* American journal of preventive medicine, 2016. **50**(4): p. 463-469.
55. Hardcastle, K., K. Ford, and M.A. Bellis, *Maternal adverse childhood experiences and their association with preterm birth: secondary analysis of data from universal health visiting.* BMC pregnancy and childbirth, 2022. **22**(1): p. 1-11.
56. Schoenaker, D.A.J.M., L.K. Callaway, and G.D. Mishra, *The Role of Childhood Adversity in the Development of Gestational Diabetes.* American Journal of Preventive Medicine, 2019. **57**(3): p. 302-310.
57. Bhengu, B.S., et al., *The role of adverse childhood experiences on perinatal substance use behaviour in KwaZulu-Natal Province, South Africa.* AIDS and Behavior, 2019: p. 1-10.
58. Leeners, B., et al., *Influence of childhood sexual abuse on pregnancy, delivery, and the early postpartum period in adult women.* Journal of psychosomatic research, 2006. **61**(2): p. 139-151.
59. Wosu, A.C., B. Gelaye, and M.A. Williams, *Maternal history of childhood sexual abuse and preterm birth: an epidemiologic review.* BMC pregnancy and childbirth, 2015. **15**(1): p. 1-9.
60. *Elwenspoek MMC, Kuehn A, Muller CP, Turner JD. The effects of early life adversity on the immune system. Psychoneuroendocrinology 2017;82:140-54.*
61. *Bick J, Zhu T, Stamoulis C, Fox NA, Zeanah C, Nelson CA. Effect of early institutionalization and foster care on long-term white matter development: a randomized clinical trial. JAMA Pediatr 2015;169:211-9.*
62. *Marini S, Davis KA, Soare TW, et al. Adversity exposure during sensitive periods predicts accelerated epigenetic aging in children. Psychoneuroendocrinology 2020;113:104484.*

63. Danese, A., *The hidden wounds of childhood trauma: Psychoneuroimmunology of early stress and the impact on mental health.* Brain and Neuroscience Advances, 2017. **1**: p. 345-346.
64. *Thaler L, Steiger H. Eating disorders and epigenetics. Adv Exp Med Biol 2017;978:93-103. .*
65. Sadeghimahalli, F., H. Zardooz, and R. Golchoobian, *Early postnatal hypothalamic-pituitary-adrenal axis activity and reduced insulin sensitivity in adult rats.* Endocrine regulations, 2019. **53**(4): p. 213-220.
66. Chen, Y.-T., et al., *Excessive glucocorticoids during pregnancy impair fetal brown fat development and predispose offspring to metabolic dysfunctions.* Diabetes, 2020. **69**(8): p. 1662-1674.
67. Bick, J. and C.A. Nelson, *Early adverse experiences and the developing brain.* Neuropsychopharmacology, 2016. **41**(1): p. 177-196.
68. Kornmeier, J. and M. Bach, *Ambiguous figures–what happens in the brain when perception changes but not the stimulus.* Frontiers in human neuroscience, 2012. **6**: p. 51.
69. Nusslock, R. and G.E. Miller, *Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis.* Biological psychiatry, 2016. **80**(1): p. 23-32.
70. Danese, A. and B.S. McEwen, *Adverse childhood experiences, allostasis, allostatic load, and age-related disease.* Physiology & behavior, 2012. **106**(1): p. 29-39.
71. Adcock, A., Bate, A., & Woodhouse, J. (2016). Effect of social media on the mental health of young people. Retrieved fromhttp://researchbriefings.parliament.uk/ResearchBriefing/Summary/CDP2016-0196.
72. Hollingsworth, K., et al., *The association between maltreatment in childhood and pre-pregnancy obesity in women attending an antenatal clinic in Australia.* PLoS One, 2012. **7**(12): p. e51868.
73. Seabrook, J.A. and W.R. Avison, *Socioeconomic status and cumulative disadvantage processes across the life course: implications for health outcomes.* Canadian Review of Sociology/Revue canadienne de sociologie, 2012. **49**(1): p. 50-68.
74. Cornelius, D.C., et al., *Inflammatory mediators: a causal link to hypertension during preeclampsia.* British journal of pharmacology, 2019. **176**(12): p. 1914-1921.
75. Rodrigo, N. and S.J. Glastras, *The emerging role of biomarkers in the diagnosis of gestational diabetes mellitus.* Journal of clinical medicine, 2018. **7**(6): p. 120.
76. Dodd, J.M., et al., *Limiting weight gain in overweight and obese women during pregnancy to improve health outcomes: the LIMIT randomised controlled trial.* BMC pregnancy and Childbirth, 2011. **11**(1): p. 1-5.
77. Poston, L., et al., *Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial.* The lancet Diabetes & endocrinology, 2015. **3**(10): p. 767-777.
78. in Pregnancy, T.I.W.M. and C. Group, *Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials.* The BMJ, 2017. **358**.
79. *Tran, N, Callaway L, Shen S, Biswas T, Scott J, Boyle F, Mamun AA. Screening for adverse childhood experiences in antenatal care settings: A scoping review. Aust N Z J Obstet Gynaecol. 2022 Jul 31. doi: 10.1111/ajo.13585. .*
80. *Gillespie RJ. Screening for Adverse Childhood Experiences in Pediatric Primary Care: Pitfalls and Possibilities. Pediatr Ann. 2019 Jul 1;48(7):e257-e261.*
81. *Campbell, T. L. (2020). Screening for adverse childhood experiences (ACEs) in primary care: A cautionary note. JAMA, 323(23), 2379-2380.*
82. *Ereyi-Osas Whitney, Racine Nicole, Sheri M. Asking about adverse childhood experiences (ACEs) in prenatal and pediatric primary care: A Narrative Review and Critique 2020.*
83. Mishra, K., et al., *Screening for adverse childhood experiences in preventive medicine settings: a scoping review.* Journal of Public Health, 2021: p. 1-10.

84. Gentry, S. and B. Paterson, *Does screening or routine enquiry for adverse childhood experiences (ACEs) meet criteria for a screening programme? A rapid evidence summary.* Journal of Public Health, 2021.
85. Courtin, E., et al., *The role of socioeconomic interventions in reducing exposure to Adverse Childhood Experiences: A systematic review.* Current Epidemiology Reports, 2019. **6**(4): p. 423-441.
86. Gervin, D.W., et al., *Centers for Disease Control and Prevention investments in adverse childhood experience prevention efforts.* American Journal of Preventive Medicine, 2022. **62**(6): p. S1-S5.

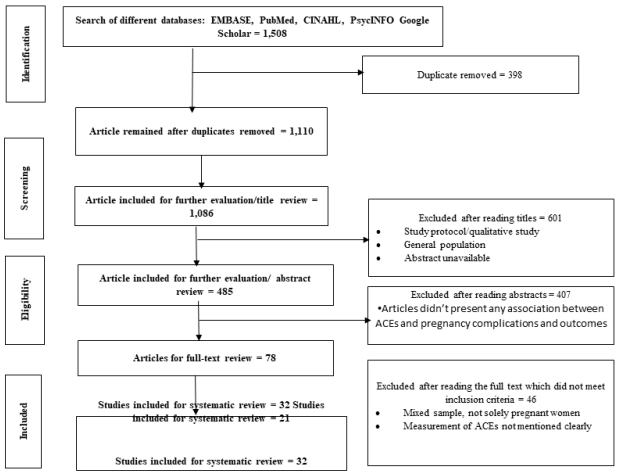
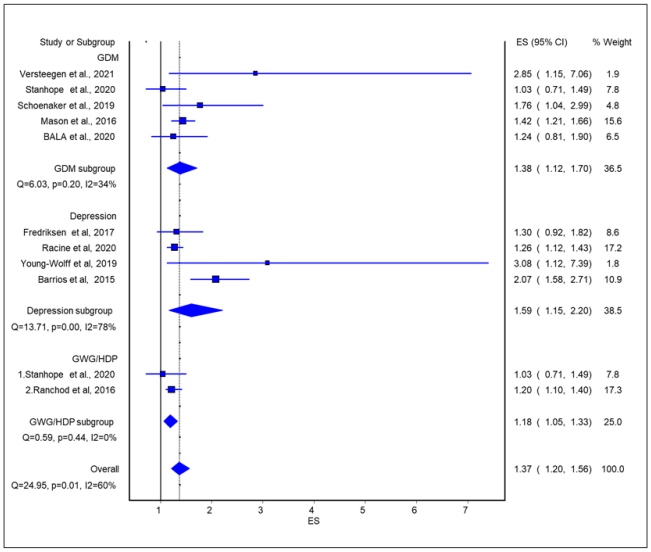
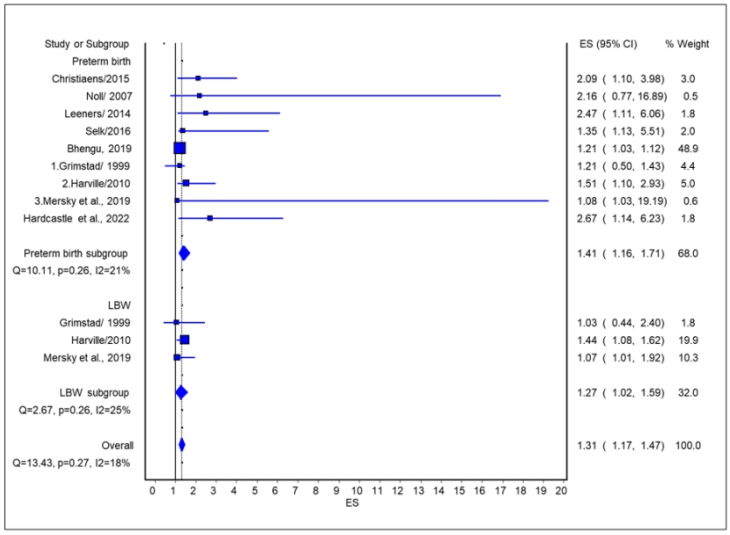


Figure-1: PRISMA diagram outlining the search strategy and selection of studies included in this review.

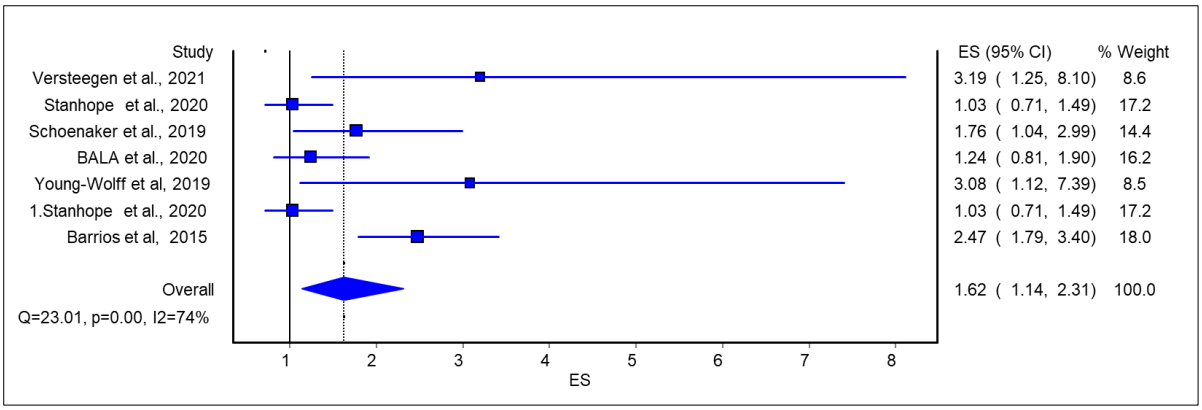
338x190mm (96 x 96 DPI)



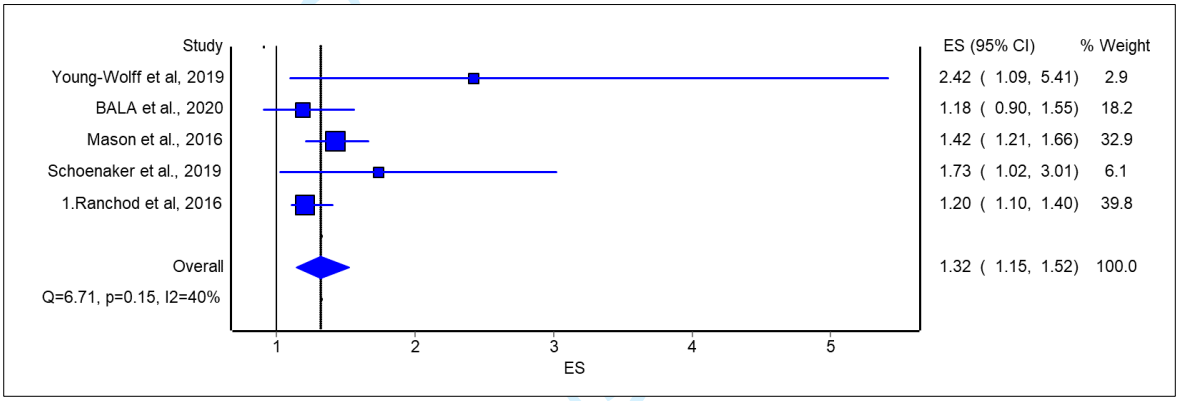
338x190mm (96 x 96 DPI)



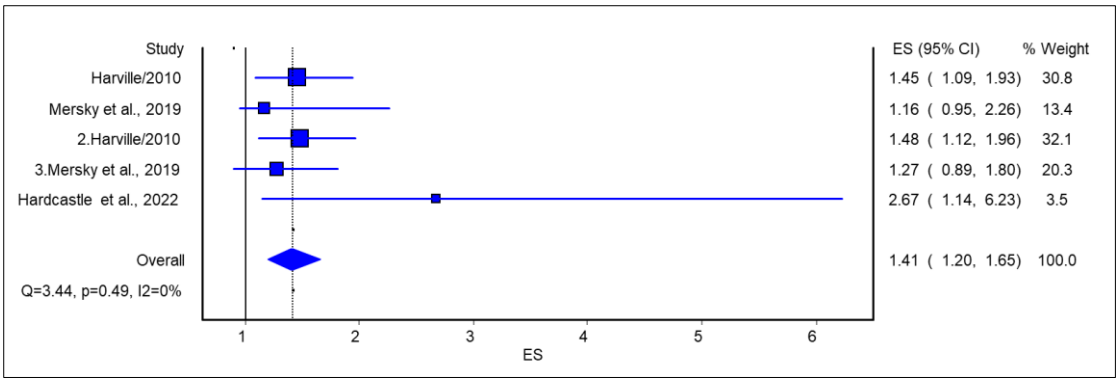
338x190mm (96 x 96 DPI)



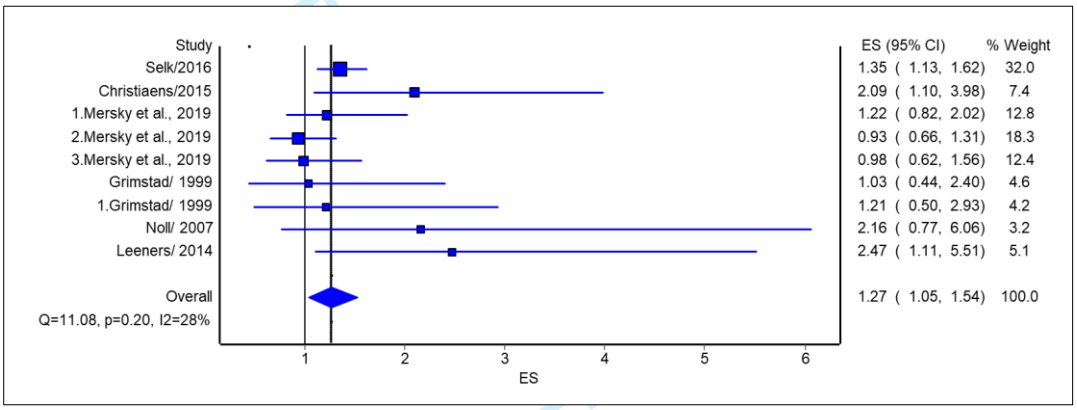
Supplementary figure -1.1: Association of ≥ 4 ACEs and adverse pregnancy complications



Supplementary figure -1.2: Association of <4 ACEs and adverse pregnancy complications



Supplementary figure -2.1: Association of ≥ 4 ACEs and adverse pregnancy outcomes



Supplementary figure -2.2: Association of <4 ACEs and adverse pregnancy outcomes

Supplementary Table S1: Search details

	#	
ACES	1	'Adverse childhood experiences'/exp OR 'adverse childhood experiences'
	2	'Childhood adversities'
	3	'Childhood abuse'
	4	'Childhood maltreatment'
	5	'Child trauma'
	6	'Adverse childhood events'
	7	'Childhood sexual abuse'
	8	'Childhood physical abuse'
	9	'Childhood mental abuse'
	10	'Childhood trauma'
	11	'Childhood violence'
	12	'Childhood hardship'
	13	'Childhood suffering'
	14	'Childhood stress'
	15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
Pregnancy complications	16	'Pregnancy complications'
	17	'depression'
	18	'anxiety'
	19	'Prenatal depression'
	20	'Depressive symptoms'
	21	'Antenatal depression'
	22	'Mental health problem'
	23	'Gestational diabetes mellitus'
	24	'GDM'
	25	'Hypertensive disorder of pregnancy'
	26	'HDP'

	27	'preeclampsia'
	28	'Maternal body weight'
	29	'Excess weight gain'
Pregnancy outcomes	30	'Abnormal fetal growth'
	31	'Intrauterine growth restriction'
	32	'Low birth weight'
	33	'LBW'
	34	'IUGR'
	35	stillbirth
	36	'Small of gestational age'
	37	'Preterm birth'
	38	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37
	39	#15 AND #38

Supplementary Table S2: Quality assessment tools

Study Quality Evaluation		
Item	**Question**	**Coding**
1. Question	Was the research question or objective in this paper clearly stated?	0-No 1-Yes
2. Population	Was the study population clearly specified and defined?	0-No 1-Yes
3. Participation	Was the participation rate of eligible persons at least 50%?	0-No 1-Yes
4. Inclusion/Exclusion Criteria	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	0-No 1-Yes
5. Sample Size	Was a sample size justification, power description, or variance and effect estimates provided?	0-No 1-Yes
6.	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	0-No 1-Yes
7. Timeframe	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	0-No 1-Yes
8. Levels of Exposure	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	0-No 1-Yes
9. Independent Variable	Were the exposure measures (independent variables) clearly defined, valid, reliable, and	0-No 1-Yes

	implemented consistently across all study participants?	
10. Longitudinal/Repeated ACEs	Was the exposure(s) assessed more than once over time?	0-No 1-Yes
11. Dependent Variable	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	0-No 1-Yes
12. Objectivity independent variable	Does the study use objective reports or multiple-methods to measure maternal ACEs? Objective measure = child abuse reports Multiple methods = self-report and corroborated reports.	0-self report 1-objective measure/multiple methods
13. Objective dependent variables	Does the study use different reporters or multiple-methods to measure maternal health/mental health outcomes? Objective measure = hospital report, diagnosis by physician, measurement by health care professional	0-self report 1-objective measure/multiple methods
14. Lost to Follow-Up	Was loss to follow-up after baseline 20% or less?	0-No 1-Yes
15. Confounder	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	0-No 1-Yes
Total	A sum of all items was calculated to obtain a total quality score (0-15).	

Supplementary Table S3: Quality of the study

SI#	First Author/Pub Date	Question	Population	Participation	Inclusion/Exclusion Criteria	Sample Size	Exposures	Timeframe	Levels of Exposure	Independent Variable	Longitudinal/Repeated ACEs	Dependent Variable	Objectivity independent variable	Objective dependent variables	Lost to Follow-Up	Confounder	Overall	Quality score
1	Christiaens/2015	1	1	0	1	1	1	1	1	1	0	0	1	0	0	1	10	Moderate
2	Grimstad/ 1999	1	1	1	1	1	1	1	0	0	0	0	1	1	0	0	9	Low
3	Hardcastle et al., 2022	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14	High
4	Noll/ 2007	1	1	1	0	0	1	1	0	0	0	0	1	1	0	0	7	Low
5	Leeners/ 2014	0	1	1	0	0	1	0	0	0	0	0	0	0	0	1	10	Moderate
6	Selk/2016	1	**1**	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
7	Harville/2010	1	1	1	0	1	1	1	1	1	1	1	0	1	0	1	12	Moderate
8	Versteegen et al., 2021	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14	High
9	Stanhope et al., 2020	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14	High
10	Schoenaker et al., 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14	High
11	Miller et al., 2017	1	1	1	1	1	1	0	0	1	0	1	0	1	0	0	9	Low
12	Mersky et al., 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
13	Mason et al., 2016	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
14	Cammack et al., 2018	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
15	BALA et al., 2020	1	1	1	1	1	1	1	0	1	0	1	1	1	0	1	12	Moderate
16	Ben Salah et al, 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	13	High
17	Bhengu, 2019	1	1	1	1	1	1	0	1	1	1	1	1	1	0	0	12	Moderate
18	Gillespie et al. (2017)	1	1	1	0	1	1	1	0	1	1	1	1	0	0	0	10	Moderate
19	Leeners et al, 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15	High
20	McDonnell and Val et al, 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	14	High
21	Shaikh et al., 2019	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	11	Moderate
22	Smith et al., 2016	1	1	1	1	0	0	1	1	1	0	1	0	0	1	1	10	Moderate
23	Ranchod et al, 2016	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	8	Low
24	Appleton et al, 2019	1	1	1	1	0	0	1	0	1	0	1	0	1	1	0	9	Low
25	Fredriksen et al, 2017	1	1	1	1	0	0	1	1	1	0	1	0	0	0	0	8	Low

26	Hantsoo et al,2019	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	8	Low
27	Letourneau et al, 2019	1	1	1	1	0	0	1	1	1	0	1	0	0	1	1	10	Moderate
28	Howell1,2020	1	1	1	1	0	1	1	1	1	1	1	0	0	1	1	12	Moderate
29	Narayan et al, 2018	1	1	1	1	0	0	1	1	1	0	1	0	0	1	0	9	Low
30	Racine et al, 2020	1	1	1	1	0	0	1	0	1	0	1	0	0	0	1	8	Low
31	Young-Wolff et al, 2019	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	11	Moderate
32	Barrios et al, 2015	1	1	1	1	0	0	1	1	1	0	1	0	1	1	1	11	Moderate

Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-14
		(b) Give reasons for non-participation at each stage	8-14
		(c) Consider use of a flow diagram	8-14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-14
		(b) Indicate number of participants with missing data for each variable of interest	8-14
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-14
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8-14
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8-14
		Cross-sectional study—Report numbers of outcome events or summary measures	8-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-14
		(*b*) Report category boundaries when continuous variables were categorized	8-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16