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

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

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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 I² 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.

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8 **77 Key questions**9
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12 **79 What is already known?**13
14 80 • Pregnant women exposed to ACEs are considered a vulnerable group because adverse
15 81 events in early life are associated with an increased risk of complications during
16 82 pregnancy and adverse birth outcomes.17
18 83 • Several systematic reviews, with or without meta-analysis, have reported associations
19 84 between ACEs and preterm birth, low birth weight, and depression/anxiety during
20 85 pregnancy.21
22 86 • None have investigated the association of ACEs and the risk of pregnancy
23 87 complications including gestational diabetes, hypertensive disorder in pregnancy,
24 88 excess gestational weight gain, depression/anxiety during pregnancy and adverse
25 89 pregnancy outcomes such as preterm birth and preterm birth and low birth weight.
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3334 **91 What are the new findings?**35
36 92 • Maternal ACEs were associated with an increased risk of pregnancy complications,
37 93 including GDM, GWG, HDP and depression/anxiety during pregnancy.38
39 94 • ACE exposure showed a significant association with any adverse pregnancy outcome.40
41 95 • For each additional unit increase in the number of ACEs, the odds of adverse
42 96 pregnancy outcomes increased 1.10 times.
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4445 **97 What do the new findings imply?**46
47 98 • Preventive strategies, screening and trauma informed care need to be examined to
48 99 improve maternal and offspring health.50
51 100 • It may be valuable to assess the role of routine ACE screening during pregnancy to
52 101 improve maternal and child health.
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104 INTRODUCTION

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

112 Early life experiences are recognized as essential determinants for health outcomes later in life
113 especially in pregnant women and their children⁷. Adverse health outcomes in pregnancy can
114 then result in intergenerational transmission of adverse health outcomes. Perhaps this occurs
115 because women who have experienced ACEs may be a vulnerable group for development of
116 health risk behaviours, including smoking, drug and alcohol use and sedentary lifestyle, along
117 with consequences of trauma such as poor sleep.⁵ These behaviours increase the risk of
118 pregnancy complications including gestational diabetes mellitus (GDM), hypertensive disorder
119 of pregnancy (HDP), excess gestational weight gain (GWG), depression/anxiety during
120 pregnancy⁸ and adverse pregnancy outcomes including low birth weight and preterm birth.⁹⁻¹¹
121 Systematic reviews have reported women who had experienced child maltreatment are more
122 likely to have pregnancy complications and that physical abuse and household substance abuse
123 were associated with greater risk of GDM^{12,13} resulting in intergenerational transmission of
124 adverse health outcomes. Overall, those reporting exposure to multiple ACEs (mostly 4 or
125 more) have an increased risk of physical, mental, and substance use disorders.¹⁴

126
127 Evidence on ACEs and the associated risk of pregnancy complications and adverse birth
128 outcomes is inconclusive. A longitudinal study in Australia reported that women exposed to
129 three or more ACEs had an elevated GDM risk.¹⁵ In contrast, a longitudinal study from the
130 USA reported no significant association between ACEs (for each score change and reported 4
131 or more ACEs) and GDM.¹⁶ A systematic review suggests that total ACEs (score in continuous
132 scale) are associated with preterm birth, although this finding needs to be confirmed in other
133 studies to explore the associations between ACEs and preterm birth using appropriate and
134 valid instruments.¹⁷ Another systematic review and meta-analysis reported that maternal
135 history of abuse before pregnancy was significantly associated with preterm delivery and low

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3 136 birth weight.¹⁸ No systematic review and meta-analysis has investigated the association of
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5 137 ACEs and the risk of pregnancy complications including GDM, HDP, GWG,
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7 138 depression/anxiety during pregnancy and adverse pregnancy outcomes. This study aims to
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9 139 systematically review and meta-analyse existing studies to establish the extent of association
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11 140 between ACEs and pregnancy complications and adverse birth outcomes. Understanding these
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13 141 associations will inform maternal clinical care and support for offspring of those women
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15 142 exposed to ACEs.
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18 144 **METHODS**

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20 145 In this systematic review and meta-analysis, we followed the Preferred Reporting Items for
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22 146 Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines¹⁹ and the Meta-
23
24 147 Analysis of Observational Studies in Epidemiology protocol²⁰ to ensure all necessary steps
25
26 148 were followed. In accordance with the guidelines, the systematic review and meta-analysis
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28 149 protocol was registered in PROSPERO (CRD42021278030).
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31 151 *Literature search strategy*

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34 152 Our search included studies published to July 10, 2021 using PubMed, EMBASE, CINAHL,
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36 153 and PsycINFO. The search strategy employed with PubMed is: (((((((((((("adverse childhood
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38 154 experiences") OR ("childhood adversities")) OR ("childhood abuse")) OR ("childhood
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40 155 maltreatment")) OR ("child trauma")) OR ("adverse childhood events")) OR ("childhood
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42 156 sexual abuse")) OR ("childhood physical abuse")) OR ("childhood mental abuse")) OR
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44 157 ("childhood trauma")) OR ("childhood violence")) OR ("childhood hardship")) OR
45
46 158 ("childhood suffering")) OR ("childhood Stress")) AND (((((((((((("pregnancy
47
48 159 complications") OR ("Depression")) OR ("Anxiety")) OR ("Prenatal depression")) OR
49
50 160 ("Depressive symptoms")) OR ("Antenatal depression")) OR ("Mental health problem")) OR
51
52 161 ("gestational diabetes mellitus")) OR ("GDM")) OR ("hypertensive disorder of pregnancy"))
53
54 162 OR ("HDP")) OR ("preeclampsia")) OR ("maternal body weight")) OR ("excess weight gain"))
55
56 163 OR ("abnormal fetal growth")) OR ("Intrauterine growth restriction")) OR (Low birth weight))
57
58 164 OR (LBW)) OR (IUGR)) OR (Stillbirth)) OR (small of gestational age)) OR ("preterm birth")).
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59 166 *Inclusion criteria*

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3 167 Studies were included if the full-text was published in English, population was pregnant
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5 168 women, reported any ACEs including childhood maltreatment (childhood physical, emotional
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7 169 and sexual abuse, childhood physical and emotional neglect and exposure to parental intimate
8
9 170 partner violence), childhood trauma or childhood hardship/suffering and if studies reported any
10
11 171 pregnancy-related complications according to National Institute of Health (NIH)²¹ (GDM,
12
13 172 HDP, GWG, depression/anxiety during pregnancy) and adverse birth outcomes such as low
14
15 173 birth weight, intra-uterine growth restriction (IUGR), preterm birth, stillbirth. Studies were
16
17 174 excluded if: (1) published in languages other than English; (2) included general population (not
18
19 175 pregnant); (3) reported reviews, qualitative studies, editorials, abstracts, case reports and letters
20
21 176 to the editor or (4) explored violence during pregnancy.
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24 178 ***Data extraction***

25 179 Two independent reviewers (TB and AAM) carried out the data extraction. If AAM and TB
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27 180 did not reach agreement, the small group (AAM, TB, LC and JS) discussed discrepancies to
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29 181 reach a consensus. A similar approach was used for full text reviews. Relevant data from each
30
31 182 of the selected studies was extracted including first author; study title; country of study; sample
32
33 183 size; study design; types of ACEs; measurement scale; and outcomes (both risk of pregnancy
34
35 184 complications and adverse pregnancy outcomes) and recorded on an Excel spreadsheet.
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38 186 **Quality assessment**

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40 187 Fifteen-point scale quality assessment tools were used to assess the quality and risk of bias of
41
42 188 the studies. We adapted a quality assessment tool from NIH “Quality Assessment Tool for
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44 189 Observational Cohort and Cross-sectional studies”.²² This tool allowed assessment of the
45
46 190 question, population, participation, inclusion/exclusion criteria, sample size, exposures,
47
48 191 timeframe, levels of exposure, independent variables, longitudinal/repeated ACEs, dependent
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50 192 variable, objectively measured independent variables, objectively measured dependent
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52 193 variables, lost to follow-up and confounders (**Supplementary Table 1**). The results of the
53
54 194 quality assessment are presented in **Supplementary Table 2**.

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3 197 ***Data Analysis***
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5 198 Analyses focused on the overall association between ACEs and risk of pregnancy
6 complications and adverse birth outcomes. Subgroup data synthesis was performed only when
7 199 three or more studies were available with the estimates for a similar type of ACE exposures.
8
9 200 ACE scores were considered on the continuous scale (for each unit change) and three
10 201 categories: i) none versus at least one ACEs; ii) one to three as low ACEs; and (iii) four or
11 202 more as high ACEs. Although most of the studies reported the odds ratio (OR) as the
12 203 measurement of association between exposures and outcomes, two studies reported relative
13 204 risk (RR) and one hazard ratio (HR). We converted all measures of associations into ORs using
14 205 conversion methods reported elsewhere.²³ In the meta-analysis, we used the quality effects
15 206 model (QE)²⁴ for bias adjustment. The advantage of the QE model is that the between-study
16 207 variability is adjusted based on the relative quality rank of the studies instead of on random
17 208 variables assigned by the random effect (RE) model. The heterogeneity of the studies was
18 209 reported by the I-squared value (I^2) that measures the proportion of total variance between
19 210 studies beyond random error.²⁴ We checked for publication bias through visualization by funnel
20 211 plot and Doi plot.²⁵ All the analyses were conducted using the MetaXL software version 5.3.²⁶
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34 214 ***Patient and Public Involvement***
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218 RESULTS

219 The literature search resulted in 1,303 records, which were screened for duplication (n=227),
220 review of titles (n=1,076) and further abstract evaluation (n=475). Finally, 32 studies met our
221 inclusion criteria for full text review, and 20 were included in meta-analysis (**Figure 1**). 75%
222 of the studies (n =24) were cohort studies and the remainder were either cross sectional or case-
223 control studies. The majority of the studies were conducted in the USA (n = 20), with fewer
224 studies from Canada (n=3), Europe (n=5) and other regions (n=4). The study sample sizes
225 varied from 48 to 11,556. The publication year ranged from 1994 to 2021. Thirteen studies
226 used the 10-item ACEs questionnaire^{8,16,27-37}, three used World Health Organization
227 (WHO) ACE-IQ questionnaires³⁸⁻⁴⁰ with one study used 8-items⁴¹ and other study used 19-
228 items questionnaire⁴² and fourteen studies used other measures^{35,43-53} (**Table-1 and 2**).

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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): <ul style="list-style-type: none"> • Genital Touch • Forced to touch the other person's genitals • Attempted Coitus; 4. Penile Vaginal Coitus 	<ul style="list-style-type: none"> • Preterm birth • Low birth weight (<2500g)
3	Noll/ 2007	USA	Cohort	186	Sexual abuse	<ul style="list-style-type: none"> • Childhood sexual abuse • Childhood sexual abuse experiences were additionally explored using questions modified from a questionnaire developed by Wyatt 	<ul style="list-style-type: none"> • Preterm birth • Preterm birth
4	Leeners/ 2014	Switzerland	Cohort	255	Sexual abuse		
5	Selk/2016	USA	Case-control	51434	Physical abuse Sexual abuse	<ul style="list-style-type: none"> • 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 number of adverse situations in childhood: <ul style="list-style-type: none"> • Financial/structural hardship • No interest in education • Family dysfunction • Lack of supportive caregiving • Violence/mental health issues • Issues of family structure • No. of hardships 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Physical abuse • Sexual abuse 	GDM

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14	Cammack et al., 2018	USA	Cohort	230	Physical abuse	Childhood Trauma Questionnaire Short-Form (CTQ)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • Preterm Birth • Low birth weight
17	Bhengu, 2019	South Africa	cross-sectional	223	ACEs	WHO-ACE IQ	<ul style="list-style-type: none"> • 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 Felitti 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.	<ul style="list-style-type: none"> • Birth weight • Shorter gestational age
23	Ranchod et al, 2016	USA	Longitudinal study	2,873	<ul style="list-style-type: none"> • 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 Felitti et al	<ul style="list-style-type: none"> • Depression • Anxiety
25	Hantsoo et al,2019	USA	Observational study	48	ACEs	10-item self-report tool developed after the original ACE study by Felitti et al	Depression
26	Howell,2019	USA	Observational study	101	ACEs	10-item self-report tool developed after the original ACE study by Felitti et al	Depression
27	Letourneau et al, 2019	Canada	Cohort	907	ACEs	10-item self-report tool developed after the original ACE study by Felitti et al	Depression
28	Narayan et al, 2018	USA	Cohort	101	ACEs	10-item self-report tool developed after the original ACE study by Felitti et al	Depression
29	Racine et al, 2020	Canada	Cohort	1994	ACEs	10-item self-report tool developed after the original ACE study by Felitti 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 Felitti 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) ACE's score (continuous)	2.09, (1.10–3.98) 1.18, (0.99–1.40)
2	Grimstad et al., 1999	Preterm birth Low birth weight	Sexual Abuse Sexual Abuse	1.03, (0.44–2.4) 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 Forced sex only	1.02, (0.88–1.17) 1.22, (1.1–1.35)
6	Harville et al., 2010	Preterm birth	Experienced both severe abuse types Financial/structural hardship No interest in education Family dysfunction Lack of supportive caregiving Violence/mental health issues Issues of family structure No. of hardships (≥ 4)	1.35, (1.13–1.62) 1.20 (0.90–1.60) 1.17 (0.93–1.48) 1.20 (0.94–1.52) 0.98 (0.81–1.19) 1.24 (0.94–1.63) 1.25 (1.02–1.54) 1.45 (1.09–1.93)
		Low birth weight	Financial/structural hardship No interest in education: Family dysfunction Lack of supportive caregiving Violence/mental health issues Issues of family structure No. of hardships (≥ 4)	1.18 (0.88–1.60) 1.18 (0.88–1.60) 1.18 (0.88–1.60) 1.18 (0.88–1.60) 1.48 (1.12–1.96) 1.48 (1.12–1.96) 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 ACEs binary	1.00 (0.84, 1.18) 1.31 (0.50, 3.39)
9	Stanhope et al., 2020	GDM HDP	ACEs 4+ Continuous ACE score ACEs 4+ Continuous ACE score:	1.03 (0.71, 1.49) 0.96 (0.88, 1.04) 1.03 (0.71, 1.49) 1.03 (0.71, 1.49)
10	Schoenaker et al., 2019	GDM	Three ACEs Four or more ACEs	1.73, (1.02, 3.01) 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 Low birthweight	ACE scores (continuous) 1 or 2 ACEs 3 or 4 ACEs 5 or more ACEs ACE scores (continuous) 1 or 2 ACEs 3 or 4 ACEs 5 or more ACEs	1.07, (1.01–1.12) 1.22 (0.79–1.89) 1.29 (0.82–2.02) 1.46 (0.95–2.26) 1.08, (1.03–1.15) 0.98 (0.62–1.56) 1.22 (0.76–1.96) 1.39 (0.88–2.19)
		Pregnancy loss	ACE scores (continuous) 1 or 2 ACEs 3 or 4 ACEs	1.12, (1.08–1.17) 0.93 (0.66–1.31) 1.27 (0.89–1.80)

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			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 studies^{8,16,35,36,50,54} 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 Australia⁵⁴ 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 studies^{27-33,37,41} 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 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=1.3, 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 diet.⁴ 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.

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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 al⁷⁵ found that ACEs screening does not excessively disrupt clinic workflow. Furthermore, they reported that ACEs

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3 screening is both acceptable for the patient and feasible for the provider. However, to determine
4 if screening for ACEs is worthwhile, studies would need to be undertaken to assess if trauma
5 informed clinical care translates to improved clinical outcomes for mother and offspring.⁷⁶
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8 There are some limitations to the current study, which reduce the generalisability of the
9 findings. Firstly, most of the included studies are from high-income western countries.
10 Secondly, due to the lack of data, we could not conduct the ACEs item-specific analysis.
11 Thirdly, the dose-response relationship in all studies could not be assessed as different studies
12 use different screening tools and cut-off values. Only five studies exploring pregnancy
13 complications and five studies investigating adverse pregnancy outcomes could be assessed for
14 a dose response relationship. Lastly, as we considered various types of ACE exposures in a
15 single review, we expected much heterogeneity in the study methodologies, populations,
16 exposures, and outcome identification. To address these limitations, the Quality Effect model,
17 which incorporates the heterogeneity of effects across the studies and reduces the risk-of-bias
18 assessment was used in the meta-analysis. Nevertheless, our study has several strengths
19 considering the comprehensive nature of the inclusion criteria, including relevant studies
20 published up to July 2021. In addition, we assessed the methodological quality of studies using
21 standard tools appropriate for observational cohort and cross-sectional studies.
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26 **CONCLUSION**

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

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3 **Ethics approval and consent to participate** Not applicable.
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5 **Data availability statement** Data are available in a public and open access repository. All
6 data analysed or produced in the study are included in the article or uploaded as supplemental
7 files.
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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

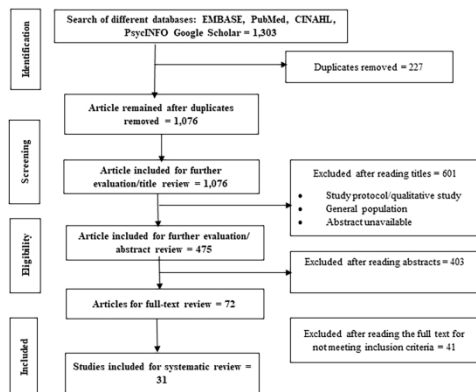
Supplementary figure -2.1: Association of ≥ 4 ACEs and adverse pregnancy outcomes

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

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

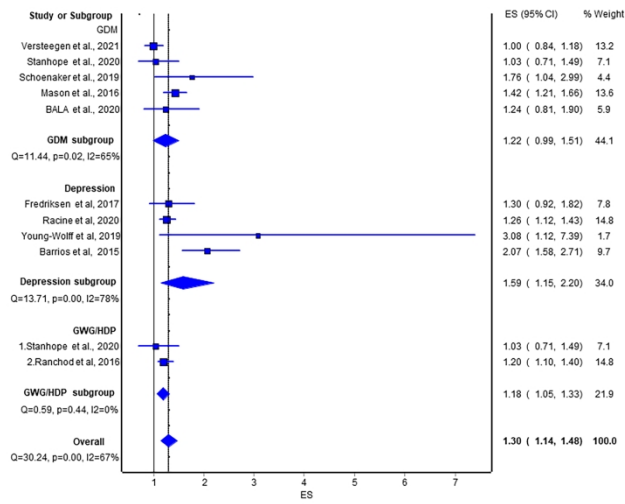
Supplementary Table 1: Quality assessment tools

Supplementary Table 2: Quality of the study

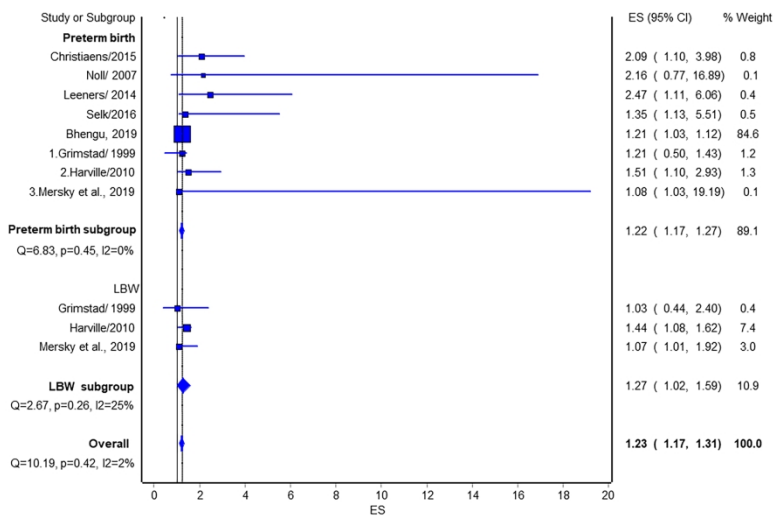


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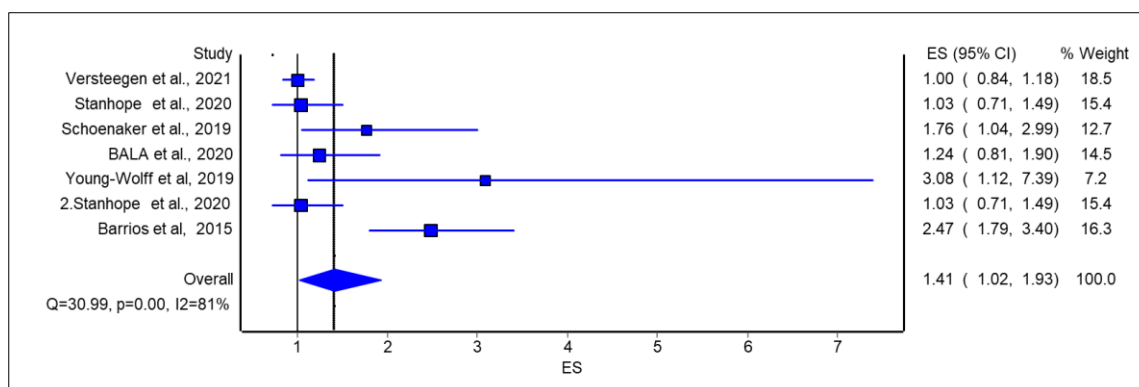
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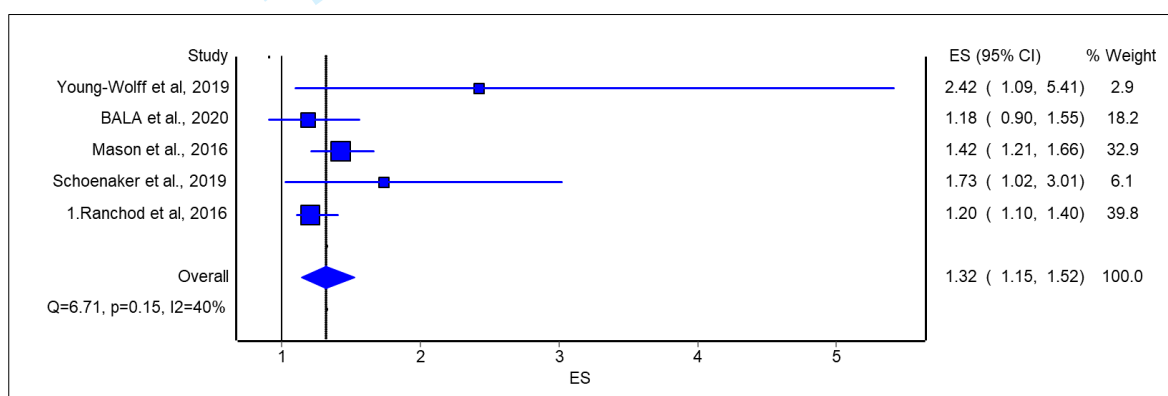
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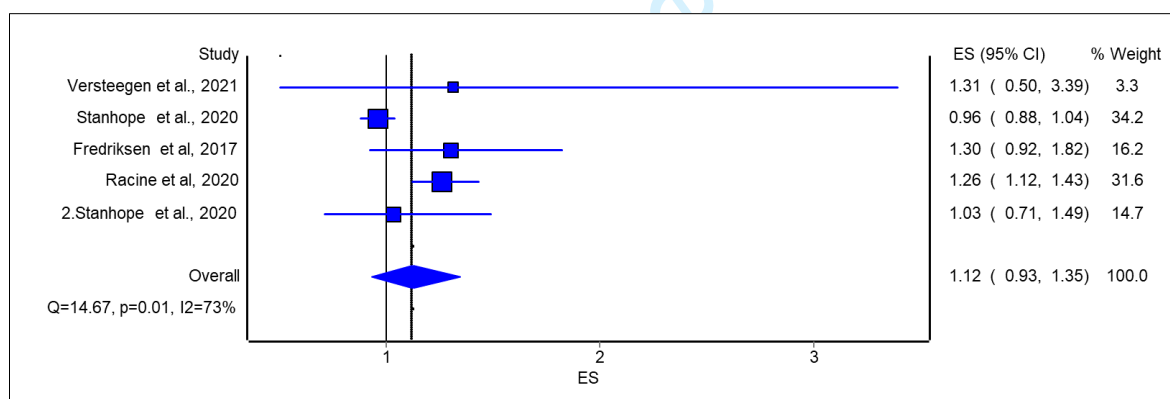
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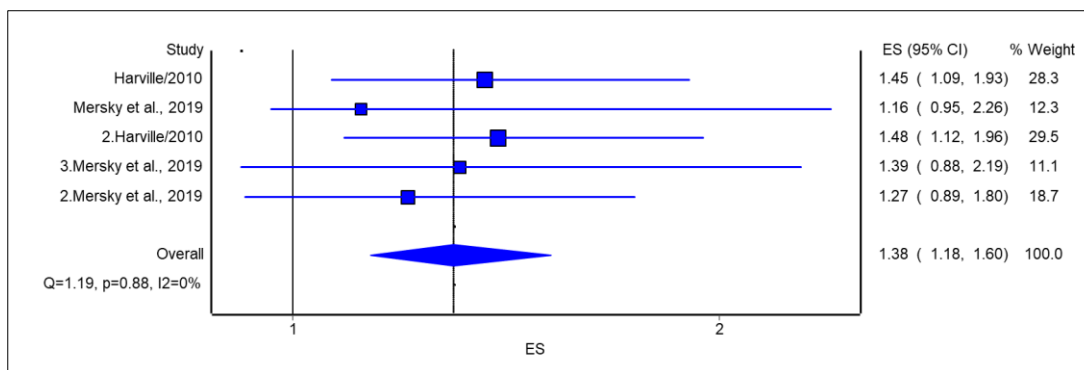
Supplementary figure -1.1: Association of ≥ 4 ACEs and adverse pregnancy complications



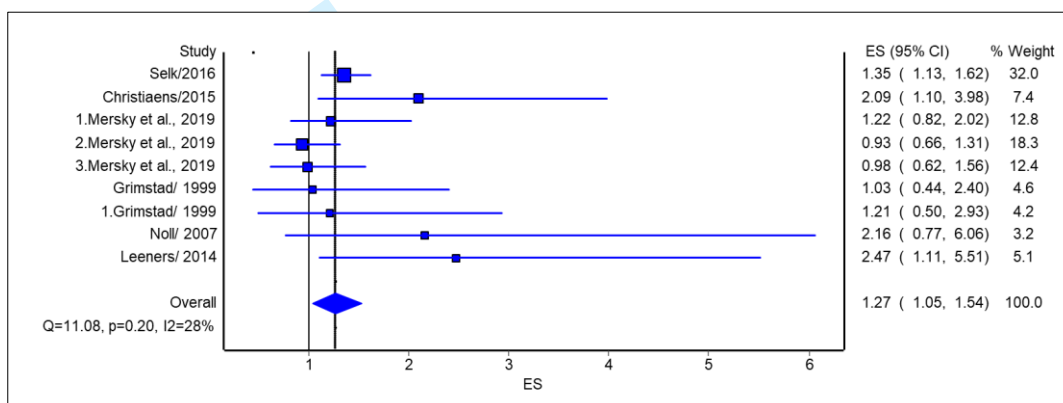
Supplementary figure -1.2: Association of < 4 ACEs and adverse pregnancy complications



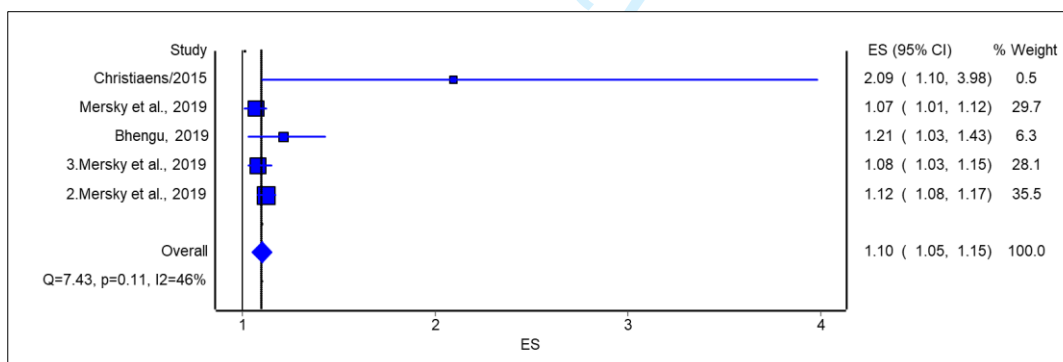
Supplementary figure -1.3: Association of ACEs (continuous scale) and adverse pregnancy complications



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

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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	7

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		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8-14
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8-14
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	8-14
		<i>Cross-sectional study</i> —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

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

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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

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6 **Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse**
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8 **Pregnancy Outcomes: A Systematic Review and Meta-analysis**
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14 51 **Abstract**

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17 52 **Background:**

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20 53 Adverse childhood experiences (ACEs) have a profound negative impact on health. However,
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22 54 the strength of the association between ACEs and pregnancy complications and adverse
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24 55 pregnancy outcomes is not well quantified or understood.
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27 56 **Objectives:**

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30 57 Conduct a systematic review and meta-analysis of the association between ACEs and risk of
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32 58 pregnancy complications and adverse pregnancy outcomes.
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35 59 **Search Strategy:**

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38 60 A comprehensive search was conducted using PubMed, EMBASE, CINAHL, PsycINFO,
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40 61 ClinicalTrials.gov and Google scholar up to July 2022.
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43 62 **Data Collection and Analysis:**

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46 63 Two reviewers independently conducted the screening and quality appraisal using a validated
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48 64 tool. Meta-analysis using the quality-effects model on the reported odds ratio (OR) was
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50 65 conducted. Heterogeneity and inconsistency were examined using the I^2 statistics.
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53 66 **Results:**

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56 67 Thirty-two studies from 1,508 met a priori inclusion criteria for systematic review, with 21
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58 68 included in the meta-analysis. Pooled analyses showed that exposure to ACEs increased the
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3 69 risk of pregnancy complications (odds ratio, OR=1.37, 95% CI: 1.20-1.50) and adverse
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5 70 pregnancy outcomes (OR=1.31, 95% CI: 1.16-1.48). In sub-group analysis, maternal ACEs
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7 71 were associated with gestational diabetes mellitus (OR=1.39, 95% CI: 1.11-1.74), antenatal
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9 72 depression (OR=1.59, 95% CI: 1.15-2.20), low offspring birth weight (OR=1.27, 95% CI:
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11 1.02-1.59), and preterm delivery (OR=1.41, 95% CI: 1.16-1.71).
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15 74 **Conclusion:**

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18 75 The results suggest that exposure to ACEs increase the risk of pregnancy complications and
19
20 76 adverse pregnancy outcomes. Preventive strategies, screening and trauma-informed care need
21
22 77 to be examined to improve maternal and child health.
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25 78 **Funding statement:** Not applicable
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27

28 79 **Keywords:** Adverse childhood experiences, pregnancy complications, adverse pregnancy
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30 80 outcomes
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33 81 **Tweetable abstract:**

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36 82 Adverse childhood experiences linked to pregnancy complications and adverse pregnancy
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38 83 outcomes
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85 **Strengths and limitations of this study**

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

94 **Introduction**

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

102
103 Early life experiences are recognized as essential determinants for health outcomes later in life
104 especially in pregnant women and their children. [7] Adverse health outcomes in pregnancy
105 can then result in intergenerational transmission of adverse health outcomes. Perhaps this
106 occurs because women who have experienced ACEs may be a vulnerable group for
107 development of health risk behaviours, including smoking, drug and alcohol use and sedentary
108 lifestyle, along with consequences of trauma such as poor sleep.[5] These behaviours increase
109 the risk of pregnancy complications including gestational diabetes mellitus (GDM),
110 hypertensive disorder of pregnancy (HDP), excess gestational weight gain (GWG),

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3 111 depression/anxiety during pregnancy [8] and adverse pregnancy outcomes including low birth
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5 112 weight and preterm birth.[9-11] Systematic reviews have reported women who had
6
7 113 experienced child maltreatment are more likely to have pregnancy complications and that
8
9 114 physical abuse and household substance abuse were associated with greater risk of GDM[12,
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11 115 13] resulting in intergenerational transmission of adverse health outcomes. Overall, those
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13 116 reporting exposure to multiple ACEs (mostly 4 or more) have an increased risk of physical,
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15 117 mental, and substance use disorders. [14]
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22 119 There is little information about ACEs and the associated risk of pregnancy complications and
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24 120 adverse birth outcomes. A longitudinal study in Australia reported that women exposed to
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26 121 three or more ACEs had an elevated GDM risk.[15] In contrast, a longitudinal study from the
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28 122 USA reported no significant association between ACEs (for each score change and reported 4
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30 123 or more ACEs) and GDM.[16] A systematic review suggests that total ACEs (score in
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32 124 continuous scale) are associated with preterm birth, although this finding needs to be confirmed
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34 125 in other studies to explore the associations between ACEs and preterm birth using appropriate
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36 126 and valid instruments.[17] Another systematic review and meta-analysis reported that maternal
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38 127 history of abuse before pregnancy was significantly associated with preterm delivery and low
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40 128 birth weight.[18] No systematic review and meta-analysis has investigated the association of
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42 129 ACEs and the risk of pregnancy complications including GDM, HDP, GWG,
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44 130 depression/anxiety during pregnancy and adverse pregnancy outcomes. This study aims to
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46 131 systematically review and meta-analyse existing studies to establish the extent of association
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48 132 between ACEs and pregnancy complications and adverse birth outcomes. Understanding these
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50 133 associations will inform maternal clinical care and support for offspring of those women
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52 134 exposed to ACEs.
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136 **Methods**

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

143 **Literature search strategy**

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

159

160 **Inclusion criteria**

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

171

172 **Data extraction**

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

180

181 **Quality assessment**

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

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3 184 Observational Cohort and Cross-sectional studies”.[22] This tool allowed assessment of the
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5 185 question, population, participation, inclusion/exclusion criteria, sample size, exposures,
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7 186 timeframe, levels of exposure, independent variables, longitudinal/repeated ACEs, dependent
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9 187 variable, objectively measured independent variables, objectively measured dependent
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11 188 variables, lost to follow-up and confounders (**Supplementary** Table S2). Overall quality score
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13 189 was considered as a continuous variable for bias adjustment in the pooled estimates. However,
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15 189 was considered as a continuous variable for bias adjustment in the pooled estimates. However,
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17 190 we have also categorised the overall quality score into three groups: 13-15 as high; 10-12 as
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19 191 moderate and <10 as low.

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22 192 The results of the quality assessment are presented in **Supplementary** Table S3.
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195 **Data Analysis**

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

213

214 **Patient and Public Involvement**

215 None

216 **Data sharing**

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

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3 219 **Results**
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6 220 The literature search resulted in 1,508 records, which were screened for duplication (n=398),
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8 221 review of titles (n=1,086) and further abstract evaluation (n=485). Finally, 32 studies met our
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10 222 inclusion criteria for systematic review, and 21 were included in meta-analysis (**Figure 1**).
11
12 223 75% of the studies were cohort studies and the remainder were either cross sectional or case-
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14 224 control studies. The majority of the studies were conducted in the USA (n = 19), with fewer
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16 225 studies from Canada (n=3), Europe (n=6) and other regions (n=5). The study sample sizes
17
18 226 varied from 48 to 11,556. The publication year ranged from 1994 to 2022. Thirteen studies
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20 227 used the 10-item ACEs questionnaire[8, 16, 27-37], three used World Health Organization
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22 228 (WHO) ACE-IQ questionnaires[38-40] with one study used 8-items [41] and two studies used
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24 229 19-items questionnaire[42, 43] and fourteen studies used other measures [35, 44-55] (**Table-**
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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 number of adverse situations in childhood: <ul style="list-style-type: none"> • 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 Felitti 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 Felitti et al
25	Hantsoo et al, 2019	USA	Observational study	48	10-item self-report tool by Felitti et al
26	Howell, 2019	USA	Observational study	101	10-item self-report tool by Felitti et al
27	Letourneau et al, 2019	Canada	Cohort	907	10-item self-report tool by Felitti et al
28	Narayan et al, 2018	USA	Cohort	101	10-item self-report tool by Felitti et al
29	Racine et al, 2020	Canada	Cohort	1994	10-item self-report tool by Felitti et al
30	Young-Wolff et al, 2019	USA	Cohort	355	10-item self-report tool by Felitti 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 Felitti et al

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3 234 In total, 32 studies were included for quality assessment. Eleven studies (34.38%) were
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5 235 assessed as high quality, 12 studies (37.50%) were assessed as moderate quality, and 9 studies
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7 236 (28.13%) were assessed as poor quality (Table S3). ACEs and risk of pregnancy complications
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10 237 ACEs and GDM: Six studies[8, 16, 35, 36, 51, 56] described an association between ACEs and
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12 238 GDM and only one study reported (**Table-2.1**). there was no association between ACEs and
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14 239 GDM [42]. A large epidemiological study in Australia [56] reported that, in pregnant women,
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16 240 exposure to any three ACEs (adjusted relative risk, aRR=1.73, 95% CI:1.0, 3.0) or four or
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18 241 more ACEs (aRR=1.70, 95% CI:1.00, 2.90) was associated with elevated GDM risk after
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20 242 adjusting preconception BMI, unhealthy diet, parity, and maternal age. Another study in the
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22 243 USA by Mason et al., 2016[35] reported that both moderate (adjusted odds ratio, aOR=1.08,
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24 244 95% CI:0.96, 1.22) and severe (aOR=1.42, 95% CI:1.21, 1.66) childhood physical abuse was
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26 245 associated with an increased risk of GDM. This study also reported that forced sexual activity
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28 246 during childhood was associated with an increased risk of GDM (aOR 1.30, 95% CI:1.14,
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30 247 1.49).
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36 248 ACEs, GWG and HDP: Only one study by Ranchod et al., 2016[54] examined the association
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38 249 between ACEs and GWG. They found that exposure to physical abuse and household alcohol
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40 250 abuse were independently associated with a 20% increase in the risk of excessive GWG. A
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42 251 study by Stanhope et al., 2020[8] found that for each ACEs score, there was a slight increase
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44 252 in the HDP risk (aOR=1.03, 95% CI:0.71, 1.49), although it was not statistically significant.
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46 253 However, they found that physical abuse (aOR= 1.22, 95% CI: 1.10-1.42) and household
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48 254 alcohol abuse (aOR= 1.21, 95% CI: 1.11-1.32) were associated with a significant increase in
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50 255 the risk of excessive GWG (**Table-2.1**).
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257 **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)
3			ACEs binary	2.85 (1.15-7.06)
4	Stanhope et al., 2020	GDM	ACEs 4+	1.03 (0.71, 1.49)
5			Continuous ACE score	0.96 (0.88, 1.04)
6		HDP	ACEs 4+	1.03 (0.71, 1.49)
7			Continuous ACE score:	1.03 (0.71, 1.49)
8	Schoenaker et al., 2019	GDM	Three ACEs	1.73, (1.02, 3.01)
9			Four or more ACEs	1.76, (1.04, 2.99)
10	Mason et al., 2016	GDM	Mild physical abuse	1.08 (0.96, 1.22)
11			Moderate physical abuse	11.16 (1.04, 1.29)
12			Severe physical abuse	1.42 (1.21, 1.66).
13			Forced sexual activity	1.30 (1.14, 1.49)
14			Combine	1.42, (1.21, 1.66)
15	BALA et al., 2020	GDM	3 or more ACEs	1.24, (0.81–1.90)
16			1–2 ACEs	1.18, (0.90– 1.55)
17	McDonnell et al, 2014	GDM		GDM not correlated with ACE indicators
18	Ranchod et al, 2016	GWG	Physical abuse	1.2, (1.1-1.4)
19			Household alcohol abuse	1.2, (1.1-1.3)
20			Household mental illness	1.1, (0.9-1.2).
21	Fredriksen et al., 2017	Depression	ACEs continuous	1.3, (0.92-1.82)
22	Hantsoo et al.,2019	Depression	< 2 ACES	EPDS (Median [IQR]): 5 [3, 6]
23			2 or more ACES	EPDS (Median [IQR]): 3 [1.5, 6.0]
24	Howell et al., 2020	Depression	ACEs continuous	Adverse childhood experiences had a direct effect on depression, B=1.11, standard error=.44, p=.01,
25	Letourneau et al, 2019	Depression	ACEs continuous	Maternal ACEs were associated with symptoms of anxiety and depression during pregnancy
26	Narayan et al et al., 2018	Depression	ACEs continuous	Maternal ACEs were associated with depression during pregnancy ($\beta = 0.32, p < 0.01$).
27	Racine et al et al., 2020	Depression	ACEs continuous	1.26, (1.12-1.43)
28	Young-Wolff et al et al., 2019	Depression	3+ ACEs	3.08, (1.12-7.39)
29			1–2 ACEs	2.42 (1.09–5.41)
30	Barrios et al., 2015	Depression		Depression: OR: 2.07; 95% CI: 1.58-2.71

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3 259 *ACEs and depression/anxiety*: Nine studies[27-33, 37, 41] examined the association between
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5 260 ACEs and depression/anxiety with almost all studies reporting a significant positive association
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7 261 during pregnancy (**Table-2.1**). For example, a large cohort study in Canada by Racine et al,
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9 262 2020[32] reported that ACEs were associated with depressive symptoms in pregnancy (aOR
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11 263 =1.26, 95% CI :1.12–1.43). Another study by Letourneau et al, 2019[30] reported that for each
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13 264 maternal ACE, there was an increased risk of symptoms of anxiety and depression during
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15 265 pregnancy. An observational study in the USA by Hantsoo et al[28, 29] reported that ACEs
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17 266 directly affected depression (B=1.1, standard error=.44, p=.01).

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25 268 *Meta-analytic results for maternal ACEs and risk of pregnancy complications:*

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28 269 A total of 11 studies (72,889 participants) were available for the quality-effect meta-analysis,
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30 270 which produced an association between maternal any ACEs and risk of any adverse pregnancy
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32 271 complications (OR=1.37, 95% CI: 1.20-1.57) (**Figure-2**). In risk factor-specific sub-analysis,
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34 272 five studies (7116 participants) were available for meta-analysis, which produced a moderate
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36 273 association between maternal ACEs and risk of GDM (OR=1.39, 95% CI: 1.11-1.74). For
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38 274 depression/anxiety during pregnancy, four studies (6116 participants) were available for this
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40 275 meta-analysis, which produced an association between maternal ACEs and risk of
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42 276 depression/anxiety during pregnancy (OR=1.5, 95% CI: 1.15-2.2). Both low (OR=1.30, 95%
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44 277 CI: 1.10-1.50) and high (OR=1.41, 95% CI: 1.02-1.90) number of ACEs were associated with
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46 278 and pregnancy complications (**Supplementary Figure S1.1 and 1.2**).

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54 280 **ACEs and adverse pregnancy outcomes**

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57 281 *ACEs and preterm birth*: Out of 31 studies, 12 [34, 38, 40, 42-48, 50, 55, 57] reported the
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59 282 association between ACEs and preterm birth(**Table-2.2**). A study in Tunisia by Ben Salah et
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3 283 al. (2019) reported that after adjustment for high-risk pregnancies, environmental tobacco
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5 284 smoke, and intra-familial ACEs, the risk of premature birth was significantly associated with
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8 285 exposure to collective violence (P-value < 0.001) and witnessing community violence (P-value
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10 286 < 0.05). In another study, Harville et al[48] reported that violence exposure during childhood
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12 287 was associated with a 44% increased risk of preterm birth (adjusted RR= 1.40; 95% CI: 1.00-
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14 288 1.90). They also found the family mental health issues increased by 24%, and a 25% increase
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17 289 in the risk of preterm birth. A case-control study in the USA by Selk et al[47] reported that
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19 290 women exposed to forced sex during childhood had a 22% greater risk of preterm birth
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21 291 (adjusted RR=1.2, 95% CI: 1.10-1.30) than those in the no exposure group. Furthermore,
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23 292 exposure to physical and sexual abuse during childhood was associated with a 35% greater risk
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25 293 of preterm birth (adjusted RR=1.30, 95% CI: 1.10-1.60). A study by Miller et al., reported that
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27 294 mothers' childhood economic hardship was independently associated with multiple adverse
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29 300 birth outcomes.[49] A study by Gillespie et al reported that maternal childhood abuse was
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31 295 associated with birth timing (birth timing was operationalized as a days gestation at birth
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33 296 continuous variable and calculated according to obstetric estimate of date of delivery and actual
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35 297 date of delivery extracted from the prenatal and labor and delivery records). [52]
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40 299 ACEs and low birth weight:

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43 300 Out of 31 studies, six [38, 42, 44, 48, 50, 53] reported an association between ACEs and low
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45 301 birth weight (**Table-2.2**).
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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, (0.88–1.17)
			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)
		Low birth weight	No. of hardships (≥ 4)	1.45 (1.09–1.93)
			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)

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3 306 Harville et al reported that violence exposure during childhood was associated with an
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5 307 increased risk of low birth weight (adjusted OR= 1.5; 95% CI: 1.1-2.0). They also found that
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7 308 violence/mental health issues (adjusted OR=1.4, 95% CI:1.1-1.9) and issues of family
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9 309 structure increased the risk of low birth weight (adjusted OR=1.4, 95% CI:1.1-1.9). A study
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11 310 by Smith et al. reported that each additional ACE decreased gestational age at birth as well as
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13 311 birth weight. [53]
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17 312 Meta-analytic results for maternal ACEs and adverse pregnancy outcomes:
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20 313 A total of 12 studies were available for this quality-effects meta-analysis, which produced an
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22 314 association between maternal ACEs and any adverse pregnancy outcomes (OR=1.31, 95% CI:
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24 315 1.17-1.47). In a sub-analysis of eight studies (59,607 participants), the quality-effects meta-
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26 316 analysis showed an association between maternal ACEs and preterm birth (OR=1.41, 95% CI:
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28 317 1.16-1.71). On the other hand, three studies (7,014 participants) were available for the quality-
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30 318 effects meta-analysis for low birth weight, which showed an association between maternal
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32 319 ACEs and low birth weight (OR=1.27, 95% CI: 1.17-1.47) (**Figure-3**). In low (one to three
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34 320 ACEs) and high (four+) ACEs specific analysis, five studies reported low ACEs exposure and
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36 321 nine studies reported high ACEs exposure. Both low (OR=1.27, 95% CI: 1.05-1.54) and high
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38 322 (OR=1.41, 95% CI: 1.20-1.65) ACE exposure showed a significant association with any
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40 323 adverse pregnancy outcome. For each additional unit increase in the number of ACEs, the odds
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42 324 of adverse pregnancy outcomes increased 1.10 times (OR=1.10, 95% CI: 1.05-1.15)
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44 325 (**Supplementary figure S2.1 and 2.2**).
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53 327 **Discussion**
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56 328 This systematic review and meta-analysis found that maternal ACEs were associated with an
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58 329 increased risk of pregnancy complications including GDM, HDP, GWG and mental health
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3 330 during pregnancy. Similarly, this study also found that maternal ACEs were associated with an
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5 331 increased risk of adverse pregnancy outcomes including preterm birth and low birth weight.
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7 332 All these associations were stronger for 4 or more compared to less than 4 ACEs. There was
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9 333 a dose-response association between ACEs and adverse pregnancy outcome. Overall, findings
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11 334 of this study suggest there is a robust association between ACEs and pregnancy complications
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13 335 and adverse pregnancy outcomes. Early prevention of ACEs might reduce the risk of pregnancy
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15 336 complications and adverse outcomes.

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19 337 To our knowledge, this is the first systematic review and meta-analysis to assess the association
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21 338 between ACEs and pregnancy complications and adverse pregnancy outcomes. A recent
22
23 339 systematic review and meta-analysis reported an association between ACEs and maternal
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25 340 depression and/or anxiety in the perinatal period (pregnancy to 1-year postpartum). [22] though
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27 341 the results of our study are not directly comparable to this study because outcomes were
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29 342 considered at different perinatal windows and results were presented differently (e.g., effect
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31 343 size vs. odds ratio). Our results on maternal ACEs and increased risk of adverse pregnancy
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33 344 outcomes are more comprehensive than previous systematic reviews [58] [59] [18] due to the
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35 345 availability of 12 recent primary studies. Overall, the direction and strength of the associations
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37 346 in our study is similar to these earlier studies [58] [59] [18].

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41 347 There could be several potential direct and indirect pathways to explain the relationship
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43 348 between ACEs and pregnancy complications and adverse pregnancy outcomes. Direct
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45 349 mechanisms may include altering the regulation of stress-signalling pathways [60] and immune
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47 350 system function[61]; changing brain structure and function; and changing the expression of
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49 351 DNA and by accelerating cellular ageing[62].For example, abuse or neglect might directly lead
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51 352 to malnutrition. Similarly, stress can directly lead to dysregulation of the
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53 353 hypothalamicpituitary-adrenal axis and associated neuro-endocrine-immune[63] as well as
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55 354 epigenetic effects[64]. Results from animal models [65, 66] and longitudinal human studies

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3 355 such as the Nurses' Health Study [35] have proposed that a strong history of ACEs may alter
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5 356 hypothalamic-pituitary-adrenal axis as reflected by elevated cortisol levels that in turn alter
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7 357 glucose metabolism and body weight regulation. Brain development begins in fetal life and
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10 358 continues into early adulthood. Early life maternal ACEs may alter the structure and function
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12 359 of the brain.[67, 68] These neurodevelopmental alterations may result in neuroendocrine
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14 360 disruption of cortisol regulation, linked to glucose metabolism [69, 70]. The experience of
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16 361 ACEs increased the risk of physical or sexual abuse during pregnancy and is associated with
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18 362 placental damage, uterine contractions, premature rupture of membranes, and genitourinary
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20 363 infections which ultimately increase the risk of preterm birth and low birth weight[71].
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22 364 Exposure to ACEs is also associated with an increased risk of health risk behaviours including
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24 365 substance use, physical inactivity and unhealthy diet[4]. Previous research has shown that
25
26 366 ACEs are associated with pre-pregnancy obesity.[72] In addition, it is also established that
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28 367 socioeconomic status and cumulative disadvantage produces health disparities across the life
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30 368 course[73]. Any of these mechanisms could explain the transgenerational nature of obesity and
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32 369 diabetes in families affected by maternal ACEs. Chronic inflammation, unhealthy behaviours,
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34 370 poor sleep and altered stress regulatory pathways are risk factors for adverse pregnancy
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36 371 complications, including GDM, HDP and depression/anxiety [74, 75]. The interplay of these
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38 372 different pathways remains largely unclear.
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48 374 According to our findings and other systematic review evidence, it may be valuable to assess
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50 375 the role of routine ACEs screening during pregnancy to improve maternal and child health.
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52 376 Trauma-informed care is not well incorporated into clinical practice guidelines. Much of the
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54 377 emphasis in maternity care is on individual behaviour change, including advice about diet,
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56 378 exercise, smoking cessation and uptake of clinical care. Approaches that do not incorporate the
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58 379 personal experiences of trauma by women attending antenatal services may inadvertently cause
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3 380 iatrogenic harm. For many years, there has been an interest in improving pregnancy outcomes
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5 381 by focusing on a limited set of physical parameters that can easily be measured such as
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7 382 gestational weight gain, without attention to the underlying mechanisms.[76, 77] Overall,
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9 383 studies of diet and exercise in pregnancy to reduce GDM, HDP and other adverse pregnancy
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11 384 outcomes have been disappointing.[78]

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15 385 A recent scoping review by Tran et al.[79] found that healthcare providers perceive that they
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17 386 are not being trained to screen for ACEs in their undergraduate training program or in their
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19 387 professional training in clinical settings. In addition, healthcare workers already have a high
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21 388 demand on their time and limited capacity to incorporate new practices without additional
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23 389 resources. There is some controversy about whether screening for ACEs is a safe and ethical
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25 390 practice, especially if the consequences of discussing ACEs (e.g. effects on mental health)
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27 391 cannot be readily addressed[80, 81]. These identified barriers are similar to those reported by
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29 392 healthcare providers in relation to ACE screening in general clinical settings[82]. Healthcare
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31 393 providers may appreciate the importance of asking about ACEs to help raise issues that
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33 394 otherwise would be unknown and unaddressed[79]. , Furthermore, Mishra et al[83] found that
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35 395 ACEs screening did not excessively disrupt clinic workflow. and was both acceptable for the
36
37 396 patient and feasible for the provider. However, to determine if screening for ACEs is
38
39 397 worthwhile, studies need to assess if trauma-informed clinical care translates to improved
40
41 398 clinical outcomes for mother and offspring. [84] Beyond screening for ACEs, our findings
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43 399 emphasise the importance of preventing ACEs in children to reduce immediate impacts as well
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45 400 as intergenerational transmission of ACEs. As well as supporting clinicians and providing
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47 401 services to address ACEs, there is growing awareness of the crucial role of upstream policy-
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49 402 and community-level interventions to improve and support positive family and social
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51 403 environments and a need for wide-scale testing of the effectiveness of such
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53 404 interventions[85][86].
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3 405 There are some limitations to the current study, which reduce the generalisability of the
4
5 406 findings. Firstly, most of the included studies are from high-income western countries.
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7 407 Secondly, due to the lack of data, we could not conduct the ACEs item-specific analysis.
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9 408 Thirdly, the dose-response relationship in all studies could not be assessed as different studies
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11 409 use different screening tools and cut-off values. Only five studies exploring pregnancy
12
13 410 complications and five studies investigating adverse pregnancy outcomes could be assessed for
14
15 411 a dose response relationship. Lastly, as we considered various types of ACE exposures in a
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17 412 single review, we expected much heterogeneity in the study methodologies, populations,
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19 413 exposures, and outcome identification. To address these limitations, the Quality Effect model,
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21 414 which incorporates the heterogeneity of effects across the studies and reduces the risk-of-bias
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23 415 assessment was used in the meta-analysis. Nevertheless, our study has several strengths
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25 416 considering the comprehensive nature of the inclusion criteria, including relevant studies
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27 417 published up to July 2021. In addition, we assessed the methodological quality of studies using
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29 418 standard tools appropriate for observational cohort and cross-sectional studies.
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36 419 **Conclusion**

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39 420 In conclusion, this systematic review and meta-analysis found that exposure to ACEs
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41 421 increases the risk of pregnancy complications and adverse pregnancy outcomes.
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43 422 Identification of women exposed to ACEs and personalising their care may provide
44
45 423 opportunities to improve maternal and child mental and physical health.
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49 424 **Contribution to authorship**

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52 425 AAM and TB contributed towards literature search, data analysis and interpretation, figures
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54 426 and tables, and writing of the manuscript. AAM, TB, LC, JS, PS contributed towards the
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56 427 drafting of the protocol, review of the study design, data collection and interpretation and
57
58 428 provided a critical review of the manuscript. AAM and SD contributed towards data
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3 429 management and analysis plan and provided oversight and interpretation of the analyses. AAM,
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5 430 DM, KT, FB, MN, MM, KM, AK, LH contributed towards the study design and editing. AAM
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7 431 and LC contributed towards the design of the manuscript, development of the protocol, and
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9 432 critical evaluation and interpretation of the results and critical review of the manuscript.
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13 433 **Disclosure of interests**

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16 434 All other authors declare no competing interests.
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20 21 436 **Details of ethics approval**

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25 437 None
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33 440 None
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41 443 Excellence for Children and Families over the Life Course.
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3 447 **Figure-1: PRISMA diagram outlining the search strategy and selection of studies**
4 448 **included in this review.**
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6 449 **Figure-2: Association of any ACE exposure with risk of pregnancy complications**
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8 450 **Figure-3: Association of any ACE exposure and adverse pregnancy outcomes**
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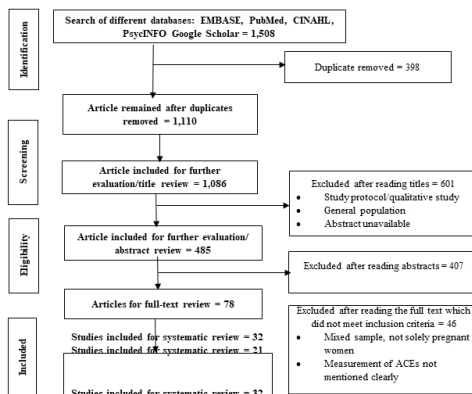
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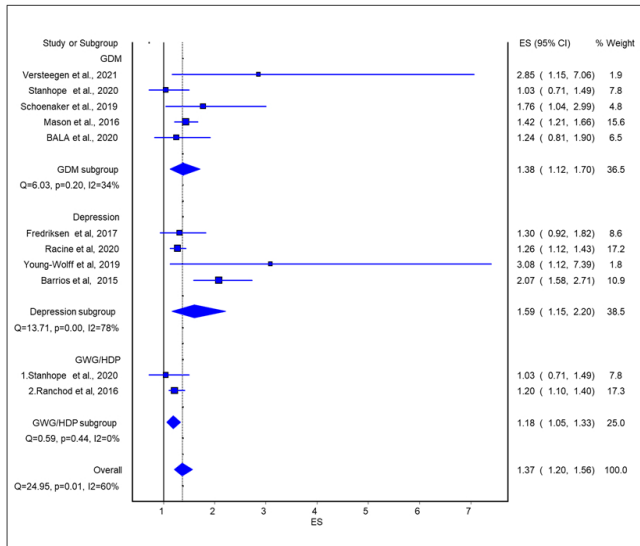
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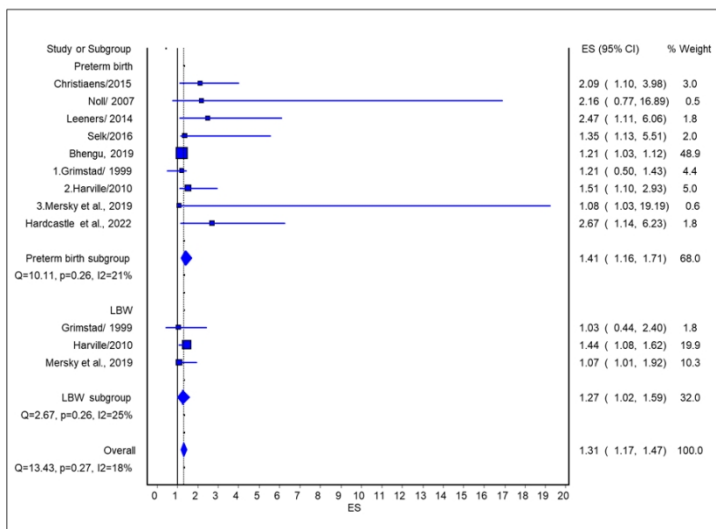


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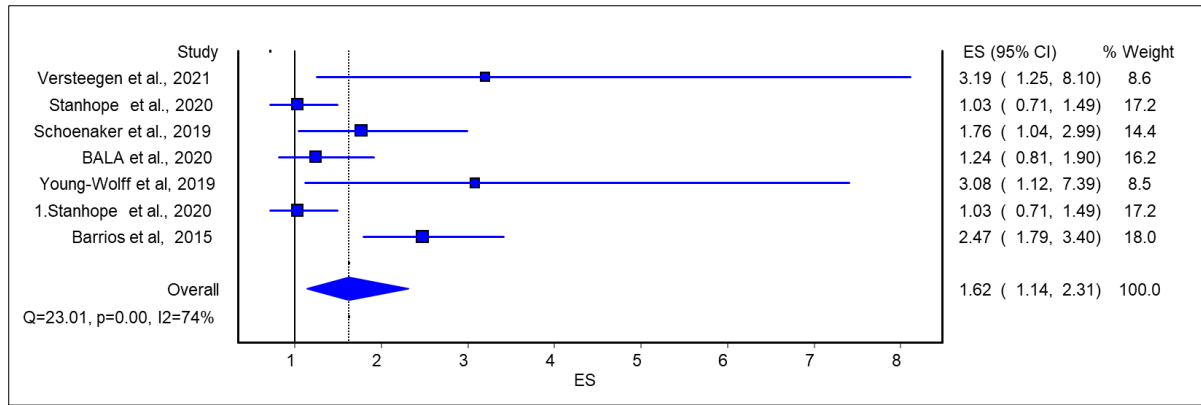
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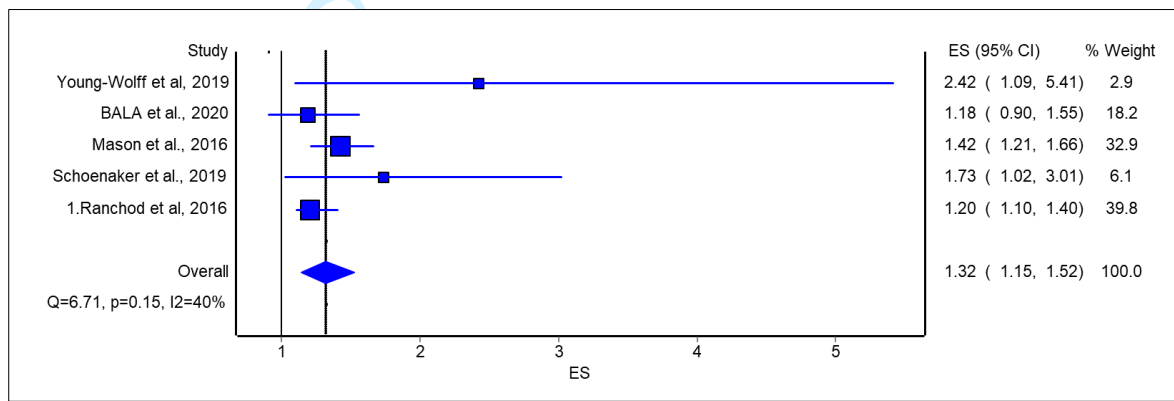
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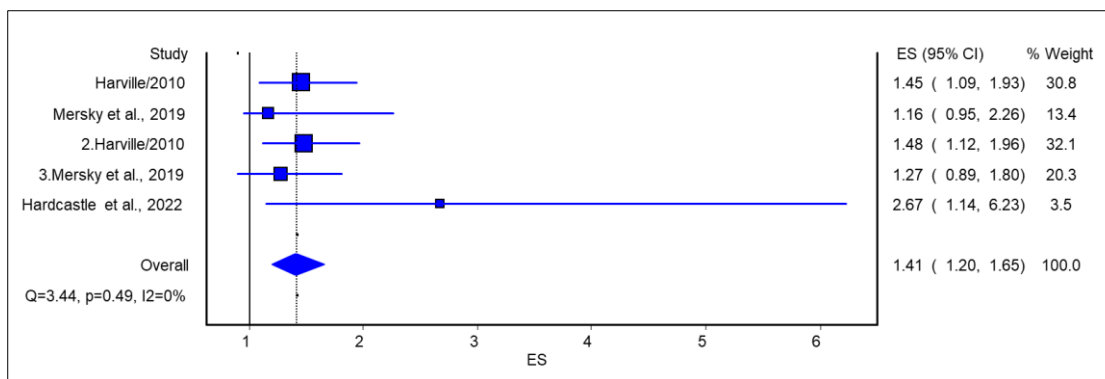
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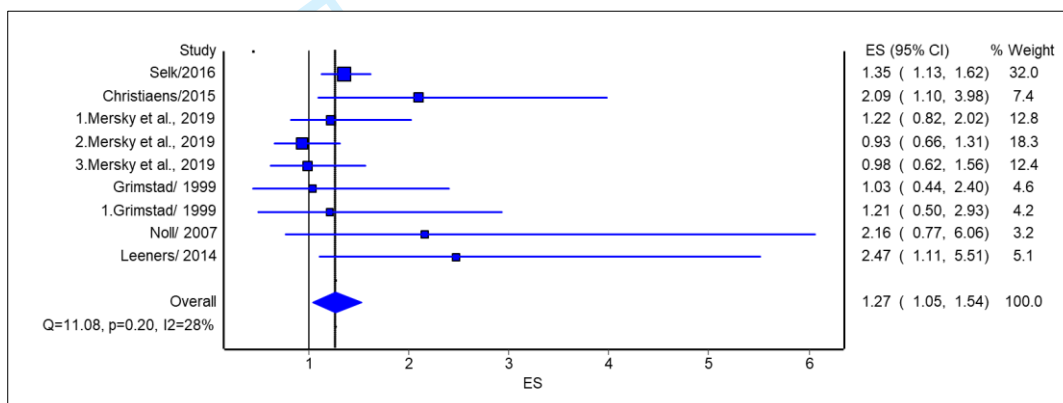
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17 **Supplementary figure -1.1: Association of ≥ 4 ACEs and adverse pregnancy complications**
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33 **Supplementary figure -1.2: Association of <4 ACEs and adverse pregnancy complications**
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Supplementary 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

Sl#	First Author/Pub Date	Question	Population	Participation	Inclusion/Exclusion Criteria	Sample Size	Exposures	Timeframe	Levels of Bias	Independent Variables	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	Bhengru, 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

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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	7

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8-14
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8-14
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	8-14
		<i>Cross-sectional study</i> —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

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

Journal:	<i>BMJ Open</i>
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

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6 **Adverse Childhood Experiences, the Risk of Pregnancy Complications and Adverse**
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8 **Pregnancy Outcomes: A Systematic Review and Meta-analysis**
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14 51 **Abstract**

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17 52 **Background:**

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20 53 Adverse childhood experiences (ACEs) have a profound negative impact on health. However,
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22 54 the strength of the association between ACEs and pregnancy complications and adverse
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24 55 pregnancy outcomes is not well quantified or understood.
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27 56 **Objectives:**

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30 57 Conduct a systematic review and meta-analysis of the association between ACEs and risk of
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32 58 pregnancy complications and adverse pregnancy outcomes.
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35 59 **Search Strategy:**

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38 60 A comprehensive search was conducted using PubMed, EMBASE, CINAHL, PsycINFO,
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40 61 ClinicalTrials.gov and Google scholar up to July 2022.
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43 62 **Data Collection and Analysis:**

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46 63 Two reviewers independently conducted the screening and quality appraisal using a validated
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48 64 tool. Meta-analysis using the quality-effects model on the reported odds ratio (OR) was
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50 65 conducted. Heterogeneity and inconsistency were examined using the I^2 statistics.
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53 66 **Results:**

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56 67 Thirty-two studies from 1,508met a priori inclusion criteria for systematic review, with twenty-
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58 68 one included in the meta-analysis. Pooled analyses showed that exposure to ACEs increased
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3 69 the risk of pregnancy complications (odds ratio, OR=1.37, 95% CI: 1.20-1.50) and adverse
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5 70 pregnancy outcomes (OR=1.31, 95% CI: 1.16-1.48). In sub-group analysis, maternal ACEs
6
7 71 were associated with gestational diabetes mellitus (OR=1.39, 95% CI: 1.11-1.74), antenatal
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9 72 depression (OR=1.59, 95% CI: 1.15-2.20), low offspring birth weight (OR=1.27, 95% CI:
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11 1.02-1.59), and preterm delivery (OR=1.41, 95% CI: 1.16-1.71).
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15 74 **Conclusion:**

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18 75 The results suggest that exposure to ACEs increase the risk of pregnancy complications and
19
20 76 adverse pregnancy outcomes. Preventive strategies, screening and trauma-informed care need
21
22 77 to be examined to improve maternal and child health.
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25 78 **Funding statement:** This research was partially supported by the Australian Research
26
27 79 Council Centre of Excellence for Children and Families over the Life Course
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29 80 (CE200100025).
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33 81 **Keywords:** Adverse childhood experiences, pregnancy complications, adverse pregnancy
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35 82 outcomes
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38 83 **Tweetable abstract:**

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40 84 Adverse childhood experiences linked to pregnancy complications and adverse pregnancy
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42 85 outcomes.
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87 **Strengths and limitations of this study**

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

96 **Introduction**

97 Adverse Childhood Experiences (ACEs)[1]are psychosocial stressors and traumas experienced
98 by an individual before 18 years of age[2, 3]The pioneering study by Felitti and colleagues
99 (1998) demonstrated that exposure to ACEs is common, ACEs co-occur and that exposure to
100 multiple ACEs are associated with an increased risk of health risk behaviours and
101 illnesses.[4]Subsequently, a growing body of research has continued to provide consistent
102 evidence that ACEs are a major public health issue due to their high prevalence and harmful
103 effects that ACEs have on human health throughout life.[5, 6]

104
105 Early life experiences are recognized as essential determinants for health outcomes later in life
106 especially in pregnant women and their children.[7]Adverse health outcomes in pregnancy can
107 then result in intergenerational transmission of adverse health outcomes. Perhaps this occurs
108 because women who have experienced ACEs may be a vulnerable group for development of
109 health risk behaviours, including smoking, drug and alcohol use and sedentary lifestyle, along
110 with consequences of trauma such as poor sleep.[5] These behaviours increase the risk of
111 pregnancy complications including gestational diabetes mellitus (GDM), hypertensive disorder
112 of pregnancy (HDP),excess gestational weight gain (GWG), depression/anxiety during

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3 113 pregnancy[8] and adverse pregnancy outcomes including low birth weight and preterm
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5 114 birth.[9-11]Systematic reviews have reported women who had experienced child maltreatment
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8 115 are more likely to have pregnancy complications and that physical abuse and household
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10 116 substance abuse were associated with greater risk of GDM[12, 13] resulting in
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12 117 intergenerational transmission of adverse health outcomes. Overall, those reporting exposure
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14 118 to multiple ACEs (mostly 4 or more) have an increased risk of physical, mental, and substance
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16 119 use disorders.[14]

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22 121 There is little information about ACEs and the associated risk of pregnancy complications and
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24 122 adverse birth outcomes. A longitudinal study in Australia reported that women exposed to
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26 123 three or more ACEs had an elevated GDM risk.[15] In contrast, a longitudinal study from the
27
28 124 USA reported no significant association between ACEs (for each score change and reported 4
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30 125 or more ACEs) and GDM.[16]A systematic review suggests that total ACEs (score in
31
32 126 continuous scale) are associated with preterm birth, although this finding needs to be confirmed
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34 127 in other studies to explore the associations between ACEs and preterm birth using appropriate
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36 128 and valid instruments.[17] Another systematic review and meta-analysis reported that maternal
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38 129 history of abuse before pregnancy was significantly associated with preterm delivery and low
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40 130 birth weight.[18] No systematic review and meta-analysis has investigated the association of
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42 131 ACEs and the risk of pregnancy complications including GDM, HDP, GWG,
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44 132 depression/anxiety during pregnancy and adverse pregnancy outcomes. This study aims to
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46 133 systematically review and meta-analyse existing studies to establish the extent of association
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48 134 between ACEs and pregnancy complications and adverse birth outcomes. Understanding these
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50 135 associations will inform maternal clinical care and support for offspring of those women
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52 136 exposed to ACEs.
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138 **Methods**

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

145 **Literature search strategy**

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

161

162 **Inclusion criteria**

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

173

174 **Data extraction**

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

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3 186 **Quality assessment**
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6 187 Fifteen-point scale quality assessment tools were used to assess the quality and risk of bias of
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8 188 the studies. We adapted a quality assessment tool from NIH “Quality Assessment Tool for
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10 189 Observational Cohort and Cross-sectional studies”.^[22] This tool allowed assessment of the
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13 190 question, population, participation, inclusion/exclusion criteria, sample size, exposures,
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15 191 timeframe, levels of exposure, independent variables, longitudinal/repeated ACEs, dependent
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17 192 variable, objectively measured independent variables, objectively measured dependent
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20 193 variables, lost to follow-up and confounders(**Supplementary** Table S2).Overall quality score
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22 194 was considered as a continuous variable for bias adjustment in the pooled estimates. However,
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24 195 we have also categorised the overall quality score into three groups: 13-15 as high;10-12 as
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26 196 moderate and <10 as low.

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29 197 The results of the quality assessment are presented in **Supplementary** Table S3.
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200 **Data Analysis**

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

218 **Patient and Public Involvement:** None.

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3 220 **Results**
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6 221 The literature search resulted in 1,508 records, which were screened for duplication (n=398),
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8 222 review of titles (n=1,086) and further abstract evaluation (n=485). Finally, 32 studies met our
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10 223 inclusion criteria for systematic review, and 21 were included in meta-analysis (**Figure 1**). 75%
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12 224 of the studies were cohort studies and the remainder were either cross sectional or case-control
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14 225 studies. The majority of the studies were conducted in the USA (n = 19), with fewer studies
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16 226 from Canada (n=3), Europe (n=6) and other regions (n=5). The study sample sizes varied from
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18 227 48 to 11,556. The publication year ranged from 1994 to 2022. Thirteen studies used the 10-
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20 228 item ACEs questionnaire[8, 16, 27-37], three used World Health Organization(WHO) ACE-
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22 229 IQ questionnaires[38-40] with one study used 8-items [41] and two studies used 19-items
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24 230 questionnaire[42, 43] and fourteen studies used other measures[35, 44-55] (**Table-1**).
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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 number of adverse situations in childhood: <ul style="list-style-type: none"> • 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	Bhengui, 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 Felitti 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 Felitti et al
25	Hantsoo et al, 2019	USA	Observational study	48	10-item self-report tool by Felitti et al
26	Howell, 2019	USA	Observational study	101	10-item self-report tool by Felitti et al
27	Letourneau et al, 2019	Canada	Cohort	907	10-item self-report tool by Felitti et al
28	Narayan et al, 2018	USA	Cohort	101	10-item self-report tool by Felitti et al
29	Racine et al, 2020	Canada	Cohort	1994	10-item self-report tool by Felitti et al
30	Young-Wolff et al, 2019	USA	Cohort	355	10-item self-report tool by Felitti 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 Felitti et al

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3 234 In total, 32 studies were included for quality assessment. Eleven studies (34.38%) were
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5 235 assessed as high quality, 12 studies (37.50%) were assessed as moderate quality, and 9 studies
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7 236 (28.13%) were assessed as poor quality (Table S3). ACEs and risk of pregnancy complications
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10 237 ACEs and GDM: Six studies [8, 16, 35, 36, 51, 56] described an association between ACEs and
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12 238 GDM and only one study reported (Table-2.1). there was no association between ACEs and
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14 239 GDM [42]. A large epidemiological study in Australia [56] reported that, in pregnant women,
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16 240 exposure to any three ACEs (adjusted relative risk, aRR=1.73, 95% CI:1.0, 3.0) or four or
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18 241 more ACEs (aRR=1.70, 95% CI:1.00, 2.90) was associated with elevated GDM risk after
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20 242 adjusting preconception BMI, unhealthy diet, parity, and maternal age. Another study in the
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22 243 USA by Mason et al., 2016 [35] reported that both moderate (adjusted odds ratio, aOR=1.08,
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24 244 95% CI:0.96, 1.22) and severe (aOR=1.42, 95% CI:1.21, 1.66) childhood physical abuse was
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26 245 associated with an increased risk of GDM. This study also reported that forced sexual activity
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28 246 during childhood was associated with an increased risk of GDM (aOR=1.30, 95% CI:1.14,
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30 247 1.49).
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36 248 ACEs, GWG and HDP: Only one study by Ranchod et al., 2016 [54] examined the association
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38 249 between ACEs and GWG. They found that exposure to physical abuse and household alcohol
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40 250 abuse were independently associated with a 20% increase in the risk of excessive GWG. A
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42 251 study by Stanhope et al., 2020 [8] found that for each ACEs score, there was a slight increase
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44 252 in the HDP risk (aOR=1.03, 95% CI:0.71, 1.49), although it was not statistically significant.
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46 253 However, they found that physical abuse (aOR= 1.22, 95% CI: 1.10-1.42) and household
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48 254 alcohol abuse (aOR= 1.21, 95% CI: 1.11-1.32) were associated with a significant increase in
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50 255 the risk of excessive GWG (Table-2.1).
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257 **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)
3			ACEs binary	2.85 (1.15-7.06)
4	Stanhope et al., 2020	GDM	ACEs 4+	1.03 (0.71, 1.49)
5			Continuous ACE score	0.96 (0.88, 1.04)
6		HDP	ACEs 4+	1.03 (0.71, 1.49)
7			Continuous ACE score:	1.03 (0.71, 1.49)
8	Schoenaker et al., 2019	GDM	Three ACEs	1.73, (1.02, 3.01)
9			Four or more ACEs	1.76, (1.04, 2.99)
10	Mason et al., 2016	GDM	Mild physical abuse	1.08 (0.96, 1.22)
11			Moderate physical abuse	11.16 (1.04, 1.29)
12			Severe physical abuse	1.42 (1.21, 1.66).
13			Forced sexual activity	1.30 (1.14, 1.49)
14			Combine	1.42, (1.21, 1.66)
15	BALA et al., 2020	GDM	3 or more ACEs	1.24, (0.81–1.90)
16			1–2 ACEs	1.18, (0.90– 1.55)
17	McDonnell et al, 2014	GDM		GDM not correlated with ACE indicators
18	Ranchod et al, 2016	GWG	Physical abuse	1.2, (1.1-1.4)
19			Household alcohol abuse	1.2, (1.1-1.3)
20			Household mental illness	1.1, (0.9-1.2).
21	Fredriksen et al., 2017	Depression	ACEs continuous	1.3, (0.92-1.82)
22	Hantsoo et al.,2019	Depression	< 2 ACES	EPDS (Median [IQR]): 5 [3, 6]
23			2 or more ACES	EPDS (Median [IQR]): 3 [1.5, 6.0]
24	Howell et al., 2020	Depression	ACEs continuous	Adverse childhood experiences had a direct effect on depression, B=1.11, standard error=.44, p=.01,
25	Letourneau et al, 2019	Depression	ACEs continuous	Maternal ACEs were associated with symptoms of anxiety and depression during pregnancy
26	Narayan et al et al., 2018	Depression	ACEs continuous	Maternal ACEs were associated with depression during pregnancy ($\beta = 0.32$, $p < 0.01$).
27	Racine et al et al., 2020	Depression	ACEs continuous	1.26, (1.12-1.43)
28	Young-Wolff et al et al., 2019	Depression	3+ ACEs	3.08, (1.12-7.39)
29			1–2 ACEs	2.42 (1.09–5.41)
30	Barrios et al., 2015	Depression		Depression: OR: 2.07; 95% CI: 1.58-2.71

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3 259 *ACEs and depression/anxiety*: Nine studies[27-33, 37, 41] examined the association between
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5 260 ACEs and depression/anxiety with almost all studies reporting a significant positive association
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7 261 during pregnancy (**Table-2.1**). For example, a large cohort study in Canada by Racine et al,
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9 262 2020[32] reported that ACEs were associated with depressive symptoms in pregnancy (aOR
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11 =1.26, 95% CI :1.12–1.43). Another study by Letourneau et al, 2019[30] reported that for each
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13 263 maternal ACE, there was an increased risk of symptoms of anxiety and depression during
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15 264 pregnancy. An observational study in the USA by Hantsoo et al[28, 29] reported that ACEs
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17 265 directly affected depression (B=1.1, standard error=.44, p=.01).
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25 268 *Meta-analytic results for maternal ACEs and risk of pregnancy complications:*

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28 269 A total of 11 studies (72,889 participants) were available for the quality-effect meta-analysis,
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30 270 which produced an association between maternal any ACEs and risk of any adverse pregnancy
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32 271 complications (OR=1.37, 95% CI: 1.20-1.57)(**Figure-2**). In risk factor-specific sub-analysis,
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34 272 five studies (7116 participants)were available for meta-analysis, which produced a moderate
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36 273 association between maternal ACEs and risk of GDM (OR=1.39, 95% CI: 1.11-1.74). For
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38 274 depression/anxiety during pregnancy, four studies (6116 participants) were available for this
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40 275 meta-analysis, which produced an association between maternal ACEs and risk of
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42 276 depression/anxiety during pregnancy (OR=1.5, 95% CI: 1.15-2.2).Both low (OR=1.30, 95%
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44 277 CI: 1.10-1.50) and high (OR=1.41, 95% CI: 1.02-1.90) number of ACEswere associated with
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46 278 and pregnancy complications (**Supplementary Figure S1.1 and 1.2**).
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54 280 **ACEs and adverse pregnancy outcomes**

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3 282 ACEs and preterm birth: Out of 31 studies, 12 [34, 38, 40, 42-48, 50, 55, 57] reported the
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5 283 association between ACEs and preterm birth(**Table-2.2**). A study in Tunisia by Ben Salah et
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7 284 al. (2019) reported that after adjustment for high-risk pregnancies, environmental tobacco
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9 285 smoke, and intra-familial ACEs, the risk of premature birth was significantly associated with
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11 286 exposure to collective violence (P-value< 0.001) and witnessing community violence (P-
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13 287 value< 0.05). In another study, Harville et al[48] reported that violence exposure during
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15 288 childhood was associated with a 44% increased risk of preterm birth (adjusted RR= 1.40; 95%
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17 289 CI: 1.00-1.90). They also found the family mental health issues increased by 24%, and a 25%
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19 290 increase in the risk of preterm birth. A case-control study in the USA by Selk et al[47] reported
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21 291 that women exposed to forced sex during childhood had a 22% greater risk of preterm birth
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23 292 (adjusted RR=1.2, 95% CI: 1.10-1.30) than those in the no exposure group. Furthermore,
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25 293 exposure to physical and sexual abuse during childhood was associated with a 35% greater risk
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27 294 of preterm birth (adjusted RR=1.30, 95% CI: 1.10-1.60). A study by Miller et al., reported that
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29 295 mothers' childhood economic hardship was independently associated with multiple adverse
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31 296 birth outcomes.[49]A study by Gillespie et al reported that maternal childhood abuse was
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33 297 associated with birth timing (birth timing was operationalized as a days gestation at birth
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35 298 continuous variable and calculated according to obstetric estimate of date of delivery and actual
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37 299 date of delivery extracted from the prenatal and labor and delivery records).[52]
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45 300 ACEs and low birth weight:

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48 301 Out of 31 studies, six [38, 42, 44, 48, 50, 53] reported an association between ACEs and low
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50 302 birth weight (**Table-2.2**).
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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, (0.88–1.17)
			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)
		Low birth weight	No. of hardships (≥ 4)	1.45 (1.09–1.93)
			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)

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3 307 Harville et al reported that violence exposure during childhood was associated with an
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5 308 increased risk of low birth weight(adjusted OR= 1.5; 95% CI: 1.1-2.0). They also found that
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7 309 violence/mental health issues (adjusted OR=1.4, 95% CI:1.1-1.9) and issues of family
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9 310 structure increased the risk of low birth weight (adjusted OR=1.4, 95% CI:1.1-1.9). A study
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11 311 by Smith et al. reported that each additional ACE decreased gestational age at birth as well as
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13 312 birth weight.[53]
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17 313 Meta-analytic results for maternal ACEs and adverse pregnancy outcomes:
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20 314 A total of 12studies were available for this quality-effects meta-analysis, which produced an
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22 315 association between maternal ACEs and any adverse pregnancy outcomes (OR=1.31, 95% CI:
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24 316 1.17-1.47). In a sub-analysis of eight studies (59,607participants), the quality-effects meta-
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26 317 analysis showed an association between maternal ACEs and preterm birth (OR=1.41, 95% CI:
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28 318 1.16-1.71). On the other hand, three studies (7,014 participants) were available for the quality-
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30 319 effects meta-analysis for low birth weight, which showed an association between maternal
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32 320 ACEs and low birth weight (OR=1.27, 95% CI: 1.17-1.47) (**Figure-3**). In low (one to three
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34 321 ACEs) and high (four+) ACEs specific analysis, five studies reported low ACEs exposure and
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36 322 nine studies reported high ACEs exposure. Both low (OR=1.27, 95% CI: 1.05-1.54) and high
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38 323 (OR=1.41, 95% CI: 1.20-1.65) ACE exposure showed a significant association with any
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40 324 adverse pregnancy outcome. For each additional unit increase in the number of ACEs, the odds
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42 325 of adverse pregnancy outcomes increased 1.10 times (OR=1.10, 95% CI: 1.05-1.15)
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44 326 (**Supplementary figure S2.1 and 2.2**).
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53 328 **Discussion**
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56 329 This systematic review and meta-analysis found that maternal ACEs were associated with an
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58 330 increased risk of pregnancy complications including GDM, HDP, GWG and mental health
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3 331 during pregnancy. Similarly, this study also found that maternal ACEs were associated with an
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5 332 increased risk of adverse pregnancy outcomes including preterm birth and low birth weight.
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8 333 All these associations were stronger for 4 or more compared to less than 4 ACEs. There was a
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10 334 dose-response association between ACEs and adverse pregnancy outcome. Overall, findings
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12 335 of this study suggest there is a robust association between ACEs and pregnancy complications
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14 336 and adverse pregnancy outcomes. Early prevention of ACEs might reduce the risk of pregnancy
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16 337 complications and adverse outcomes.

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19 338 To our knowledge, this is the first systematic review and meta-analysis to assess the association
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21 339 between ACEs and pregnancy complications and adverse pregnancy outcomes. A recent
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23 340 systematic review and meta-analysis reported an association between ACEs and maternal
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25 341 depression and/or anxiety in the perinatal period (pregnancy to 1-year postpartum). [22] though
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27 342 the results of our study are not directly comparable to this study because outcomes were
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29 343 considered at different perinatal windows and results were presented differently (e.g., effect
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31 344 size vs. odds ratio). Our results on maternal ACEs and increased risk of adverse pregnancy
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33 345 outcomes are more comprehensive than previous systematic reviews [58][59][18] due to the
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35 346 availability of 12 recent primary studies. Overall, the direction and strength of the associations
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37 347 in our study is similar to these earlier studies [58][59][18].

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39 348 There could be several potential direct and indirect pathways to explain the relationship
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41 349 between ACEs and pregnancy complications and adverse pregnancy outcomes. Direct
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43 350 mechanisms may include altering the regulation of stress-signalling pathways [60] and immune
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45 351 system function[61]; changing brain structure and function; and changing the expression of
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47 352 DNA and by accelerating cellular ageing[62]. For example, abuse or neglect might directly lead
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49 353 to malnutrition. Similarly, stress can directly lead to dysregulation of the hypothalamic
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51 354 pituitary-adrenal axis and associated neuro-endocrine-immune[63] as well as epigenetic
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53 355 effects[64]. Results from animal models [65, 66] and longitudinal human studies such as the
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3 356 Nurses' Health Study[35] have proposed that a strong history of ACEs may alter hypothalamic-
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5 357 pituitary-adrenal axis as reflected by elevated cortisol levels that in turn alter glucose
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7 358 metabolism and body weight regulation. Brain development begins in fetal life and continues
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10 359 into early adulthood. Early life maternal ACEs may alter the structure and function of the
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12 360 brain.[67, 68] These neurodevelopmental alterations may result in neuroendocrine disruption
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14 361 of cortisol regulation, linked to glucose metabolism [69, 70]. The experience of ACEs
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16 362 increased the risk of physical or sexual abuse during pregnancy and is associated with placental
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18 363 damage, uterine contractions, premature rupture of membranes, and genitourinary infections
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20 364 which ultimately increase the risk of preterm birth and low birth weight[71]. Exposure to ACEs
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22 365 is also associated with an increased risk of health risk behaviours including substance use,
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24 366 physical inactivity and unhealthy diet[4]. Previous research has shown that ACEs are
25
26 367 associated with pre-pregnancy obesity.[72]In addition, it is also established that socioeconomic
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28 368 status and cumulative disadvantage produces health disparities across the life course[73]. Any
29
30 369 of these mechanisms could explain the transgenerational nature of obesity and diabetes in
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32 370 families affected by maternal ACEs. Chronic inflammation, unhealthy behaviours, poor sleep
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34 371 and altered stress regulatory pathways are risk factors for adverse pregnancy complications,
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36 372 including GDM, HDP and depression/anxiety [74, 75]. The interplay of these different
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38 373 pathways remains largely unclear.
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48 375 According to our findings and other systematic review evidence, it may be valuable to assess
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50 376 the role of routine ACEs screening during pregnancy to improve maternal and child health.
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52 377 Trauma-informed care is not well incorporated into clinical practice guidelines. Much of the
53
54 378 emphasis in maternity care is on individual behaviour change, including advice about diet,
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56 379 exercise, smoking cessation and uptake of clinical care. Approaches that do not incorporate the
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58 380 personal experiences of trauma by women attending antenatal services may inadvertently cause
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3 381 iatrogenic harm. For many years, there has been an interest in improving pregnancy outcomes
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5 382 by focusing on a limited set of physical parameters that can easily be measured such as
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7 383 gestational weight gain, without attention to the underlying mechanisms.[76, 77] Overall,
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9 384 studies of diet and exercise in pregnancy to reduce GDM, HDP and other adverse pregnancy
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11 385 outcomes have been disappointing.[78]

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15 386 A recent scoping review by Tran et al.[79] found that healthcare providers perceive that they
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17 387 are not being trained to screen for ACEs in their undergraduate training program or in their
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19 388 professional training in clinical settings. In addition, healthcare workers already have a high
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21 389 demand on their time and limited capacity to incorporate new practices without additional
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23 390 resources. There is some controversy about whether screening for ACEs is a safe and ethical
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25 391 practice, especially if the consequences of discussing ACEs (e.g. effects on mental health)
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27 392 cannot be readily addressed[80, 81]. These identified barriers are similar to those reported by
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29 393 healthcare providers in relation to ACE screening in general clinical settings[82]. Healthcare
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31 394 providers may appreciate the importance of asking about ACEs to help raise issues that
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33 395 otherwise would be unknown and unaddressed[79]. Furthermore, Mishra et al[83] found that
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35 396 ACEs screening did not excessively disrupt clinic workflow. and was both acceptable for the
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37 397 patient and feasible for the provider. However, to determine if screening for ACEs is
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39 398 worthwhile, studies need to assess if trauma-informed clinical care translates to improved
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41 399 clinical outcomes for mother and offspring.[84]Beyond screening for ACEs, our findings
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43 400 emphasise the importance of preventing ACEs in children to reduce immediate impacts as well
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45 401 as intergenerational transmission of ACEs. As well as supporting clinicians and providing
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47 402 services to address ACEs, there is growing awareness of the crucial role of upstream policy-
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49 403 and community-level interventions to improve and support positive family and social
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51 404 environments and a need for wide-scale testing of the effectiveness of such
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53 405 interventions[85][86].
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3 406 There are some limitations to the current study, which reduce the generalisability of the
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5 407 findings. Firstly, most of the included studies are from high-income western countries.
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7 408 Secondly, due to the lack of data, we could not conduct the ACEs item-specific analysis.
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9 409 Thirdly, the dose-response relationship in all studies could not be assessed as different studies
10
11 410 use different screening tools and cut-off values. Only five studies exploring pregnancy
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13 411 complications and five studies investigating adverse pregnancy outcomes could be assessed for
14
15 412 a dose response relationship. Lastly, as we considered various types of ACE exposures in a
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17 413 single review, we expected much heterogeneity in the study methodologies, populations,
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19 414 exposures, and outcome identification. To address these limitations, the Quality Effect model,
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21 415 which incorporates the heterogeneity of effects across the studies and reduces the risk-of-bias
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23 416 assessment was used in the meta-analysis. Nevertheless, our study has several strengths
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25 417 considering the comprehensive nature of the inclusion criteria, including relevant studies
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27 418 published up to July 2021. In addition, we assessed the methodological quality of studies using
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29 419 standard tools appropriate for observational cohort and cross-sectional studies.
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36 420 **Conclusion**

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39 421 In conclusion, this systematic review and meta-analysis found that exposure to ACEs
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41 422 increases the risk of pregnancy complications and adverse pregnancy outcomes.
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43 423 Identification of women exposed to ACEs and personalising their care may provide
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45 424 opportunities to improve maternal and child mental and physical health.
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49 425 **Contribution to authorship**

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51
52 426 AAM and TB contributed towards literature search, data analysis and interpretation, figures
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54 427 and tables, and writing of the manuscript. AAM, TB, LC, JS, PS contributed towards the
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56 428 drafting of the protocol, review of the study design, data collection and interpretation and
57
58 429 provided a critical review of the manuscript. AAM and SD contributed towards data
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3 430 management and analysis plan and provided oversight and interpretation of the analyses. AAM,
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5 431 DM, KT, FB, MN, MM, KM, AK, LH contributed towards the study design and editing. AAM
6
7 432 and LC contributed towards the design of the manuscript, development of the protocol, and
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9 433 critical evaluation and interpretation of the results and critical review of the manuscript.
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13 434 **Disclosure of interests**

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16 435 All other authors declare no competing interests.
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20 21 437 **Details of ethics approval**

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25 438 None
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34
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38 443 Data Availability: No additional data available.
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3 447 **Figure-1: PRISMA diagram outlining the search strategy and selection of studies**
4 448 **included in this review.**
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6 449 **Figure-2: Association of any ACE exposure with risk of pregnancy complications**
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8 450 **Figure-3: Association of any ACE exposure and adverse pregnancy outcomes**
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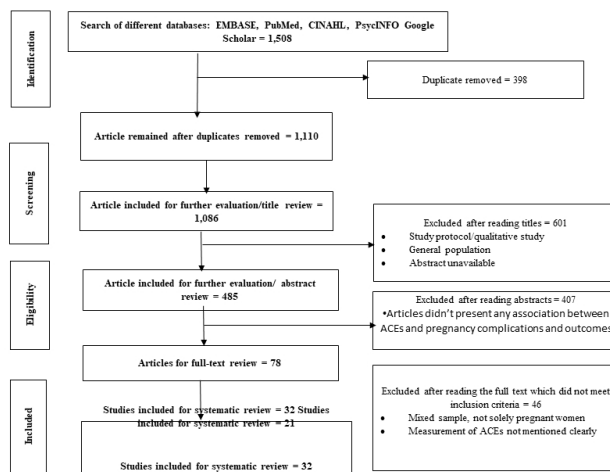
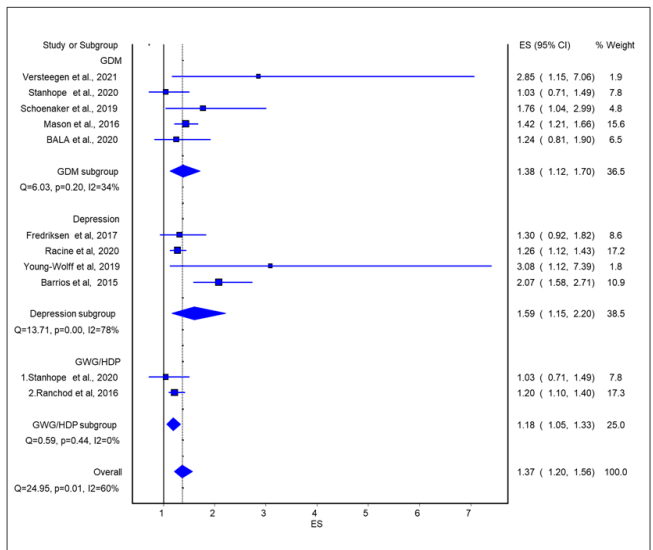


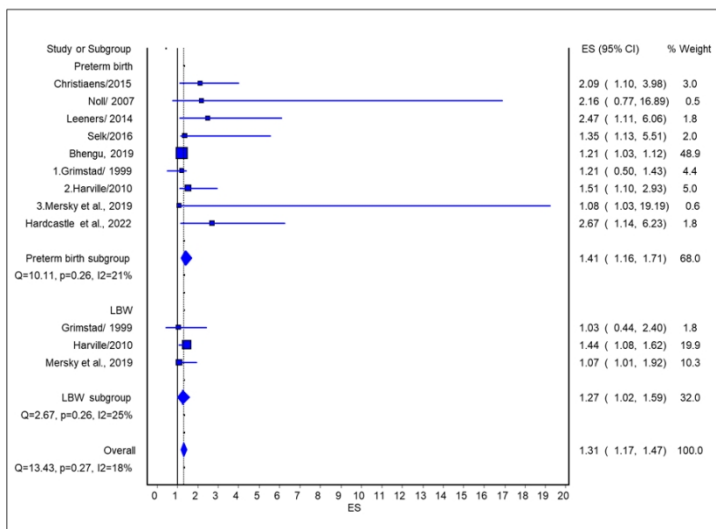
Figure-1: PRISMA diagram outlining the search strategy and selection of studies included in this review.

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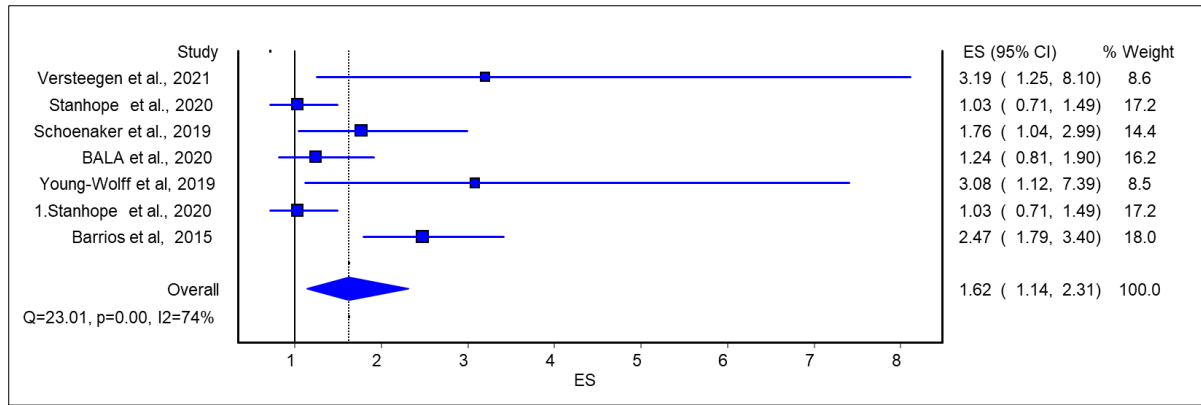
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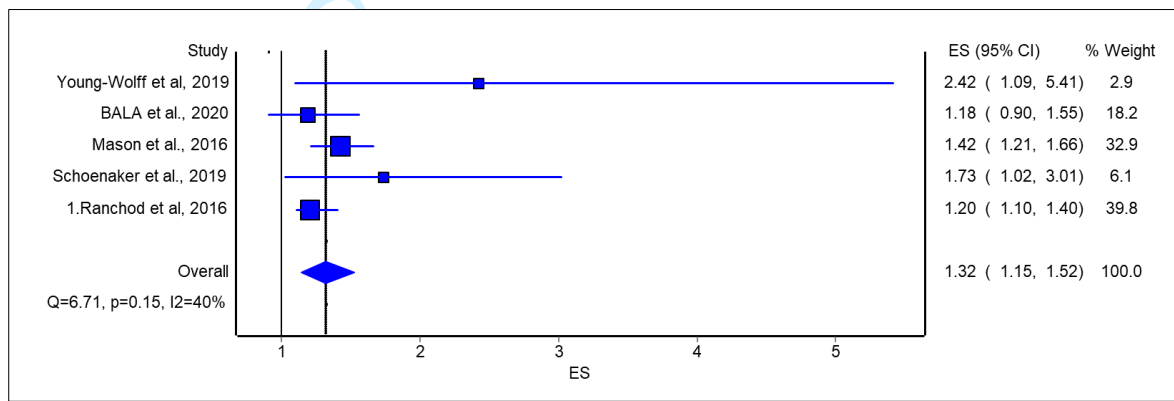
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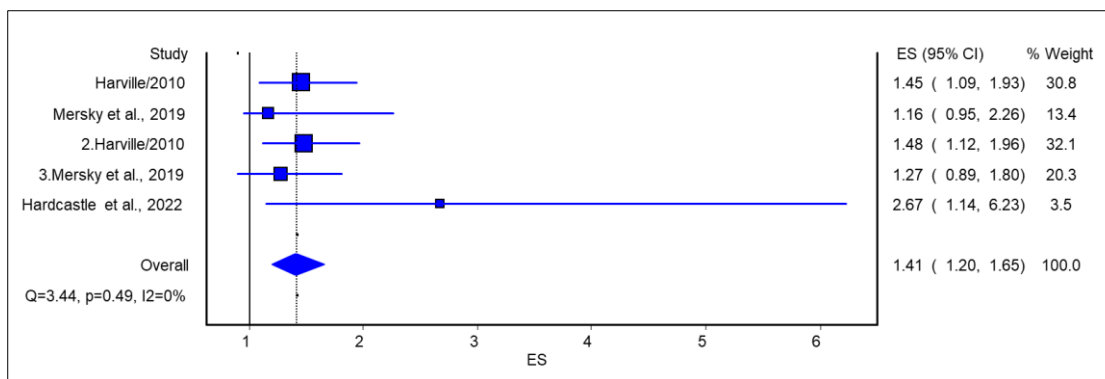
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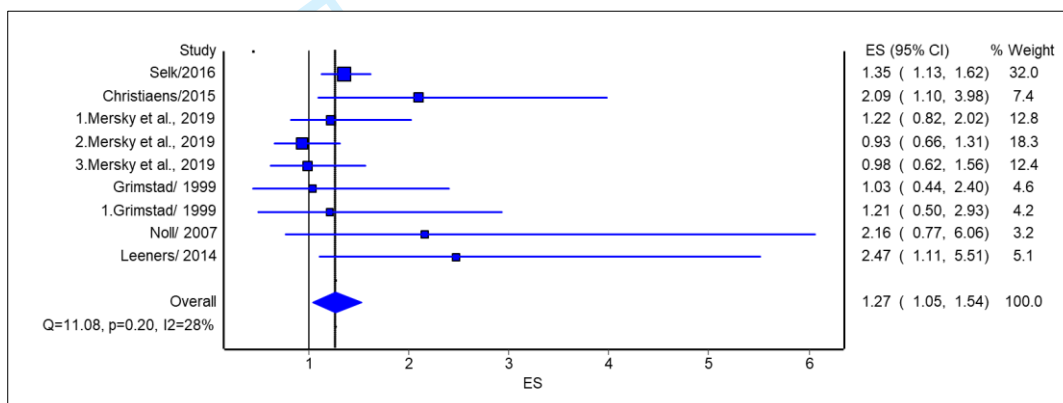
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17 **Supplementary figure -1.1: Association of ≥ 4 ACEs and adverse pregnancy complications**
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33 **Supplementary figure -1.2: Association of < 4 ACEs and adverse pregnancy complications**
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Supplementary 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

Sl#	First Author/Pub Date	Question	Population	Participation	Inclusion/Exclusion Criteria	Sample Size	Exposures	Timeframe	Levels of Bias	Independent Variables	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	Bhengru, 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

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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	7

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		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8-14
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8-14
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	8-14
		<i>Cross-sectional study</i> —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