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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

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

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

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

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

Results 32 studies from 1508 met a priori inclusion criteria for systematic review, with 21 included in the meta-analysis. Pooled analyses showed that exposure to ACEs increased the risk of pregnancy complications (OR 1.37, 95% CI 1.20 to 1.57) and adverse pregnancy outcomes (OR 1.31, 95% CI 1.17 to 1.47). In sub-group analysis, maternal ACEs were associated with gestational diabetes mellitus (OR 1.39, 95% CI 1.11 to 1.74), antenatal depression (OR 1.59, 95% CI 1.15 to 2.20), low offspring birth weight (OR 1.27, 95% CI 1.02 to 1.47), and preterm delivery (OR 1.41, 95% CI 1.16 to 1.71).

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

INTRODUCTION

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

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

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

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

METHODS

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

Literature search strategy

Our search included studies published to July 2022 using PubMed, Embase, CINAHL, PsycINFO, ClinicalTrials.gov and Google scholar. The search strategy employed with PubMed is: 'adverse childhood experiences' OR 'childhood adversities' OR 'childhood abuse' OR 'childhood maltreatment' OR 'child trauma' OR 'adverse childhood events' OR 'childhood sexual abuse' OR 'childhood physical abuse' OR 'childhood mental abuse' OR 'childhood trauma' OR 'childhood violence' OR 'childhood hardship' OR 'childhood suffering' OR 'childhood stress' AND 'pregnancy complications' OR 'depression' OR 'anxiety' OR 'prenatal depression' OR 'depressive symptoms' OR 'antenatal depression' OR 'mental health problem' OR 'gestational diabetes mellitus' OR 'GDM' OR 'hypertensive disorder of pregnancy' OR 'HDP' OR 'preeclampsia' OR 'maternal body weight' OR 'excess weight gain' OR 'abnormal fetal growth' OR 'intrauterine growth restriction' OR 'low birth weight' OR 'LBW' OR 'IUGR' OR 'stillbirth' OR 'small for gestational age' OR 'preterm birth'. These search details are presented in a online supplemental table S1.

Inclusion criteria

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

Data extraction

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

Quality assessment

Fifteen-point scale quality assessment tools were used to assess the quality and risk of bias of the studies. We adapted a quality assessment tool from the NIH 'Quality Assessment Tool for Observational Cohort and Cross-sectional studies'.[22] This tool allowed assessment of the question, population, participation, inclusion/exclusion criteria, sample size, exposures, timeframe, levels of exposure, independent variables,

longitudinal/repeated ACEs, dependent variable, objectively measured independent variables, objectively measured dependent variables, lost to follow-up and confounders (online supplemental table S2). Overall quality score was considered as a continuous variable for bias adjustment in the pooled estimates. However, we have also categorised the overall quality score into three groups: 13–15 as high; 10–12 as moderate; and <10 as low.

The results of the quality assessment are presented in online supplemental table S3.

Data analysis

Meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Analyses focused on the overall association between ACEs and risk of pregnancy complications and adverse birth outcomes. Subgroup data synthesis was performed only when three or more studies were available with the estimates for a similar type of ACE exposures. ACE scores were considered on the continuous scale (for each unit change) and three categories: (1) none versus one ACE; (2) two to three ACEs (low ACEs); and (3) four or more ACEs (high ACEs). Although most of the studies reported the odds ratio (OR) as the measurement of association between exposures and outcomes, two studies reported relative risk (RR) and one study reported hazard ratio (HR). We converted all measures of associations into ORs using conversion methods reported elsewhere.[23] In the meta-analysis, we used the quality effects model (QE)[24] for bias adjustment. The advantage of the QE model is that the between-study variability is adjusted based on the relative quality rank of the studies instead of on random variables assigned by the random effect model. The heterogeneity of the studies was reported by the I^2 value that measures the proportion of total variance between studies beyond random error.[24] We checked for publication bias through visualisation by funnel plot and Doi plot.[25] All the analyses were conducted using the MetaXL software version 5.3.[26]

RESULTS

The literature search resulted in 1508 records, which were screened for duplication (n=398), review of titles (n=1086) and further abstract evaluation (n=485). Finally, 32 studies met our inclusion criteria for systematic review, and 21 were included in the meta-analysis (figure 1). Seventy-five percent of the studies were cohort studies and the remainder were either cross sectional or case–control studies. The majority of the studies were conducted in the USA (n=19), with fewer studies from Canada (n=3), Europe (n=6) and other regions (n=5). The study sample sizes varied from 48 to 11 556. The publication year ranged from 1994 to 2022. Thirteen studies used the 10-item ACEs questionnaire,[8 16 27–37] three used the WHO ACE-IQ questionnaires,[38–40] one study used 8-items[41] and two studies used 19-items questionnaire,[42 43] and 14 studies used other measures[35 44–55] (table 1).

In total, 32 studies were included for quality assessment. Eleven studies (34.38%) were assessed as high quality, 12 studies (37.50%) were assessed as moderate quality, and nine studies (28.13%) were assessed as poor quality (online supplemental table S3).

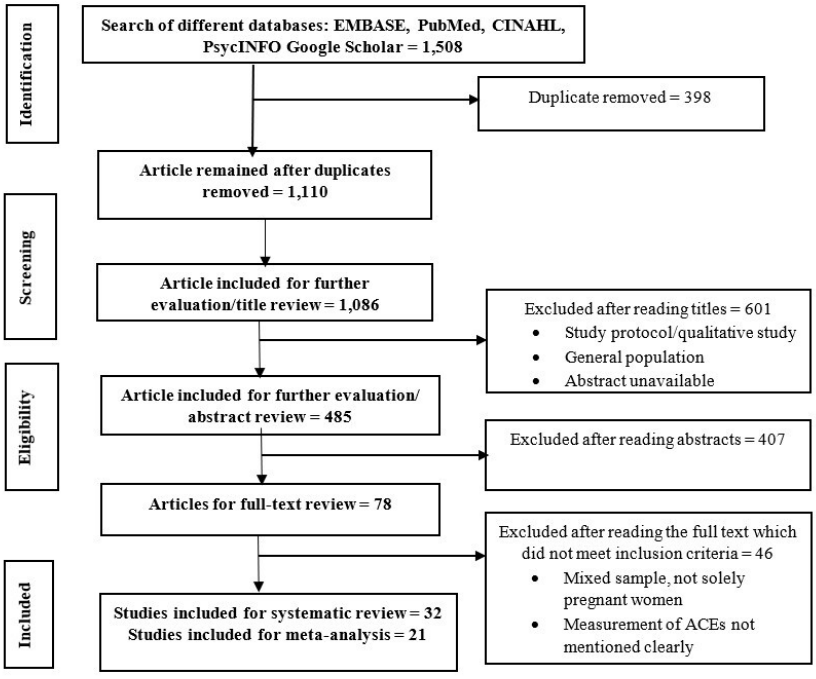

Figure-1: PRISMA diagram outlining the search strategy and selection of studies included in this review.

Figure 1 PRISMA diagram outlining the search strategy and selection of studies included in this review. ACEs, adverse childhood experiences; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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 *et al*, 2015[34]	Canada	Case–control	622	10-item self-report tool by Felliti *et al*
2	Grimstad *et al*, 1999[44]	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; penile vaginal coitus
3	Noll *et al*, 2007[45]	USA	Cohort	186	Childhood sexual abuse
4	Leeners *et al*, 2014[46]	Switzerland	Cohort	255	Childhood sexual abuse experiences were additionally explored using questions modified by Wyatt
5	Selk *et al*, 2016[47]	USA	Case–control	51 434	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 *et al*, 2010[48]	UK	Cohort	4865	The phrase 'childhood hardship' is used herein to refer to a number of adverse situations in childhood: ► Financial/structural hardship ► No interest in education ► Family dysfunction ► Lack of supportive caregiving ► Violence/mental health issues ► Issues of family structure ► Number of hardships
7	Appleton *et al*, 2019[37]	USA	Cohort study	126	10-item self-report tool by Felliti *et al*
8	Versteegen *et al*, 2021[16]	USA	Cohort	30	10-item self-report tool by Felliti *et al*
9	Stanhope *et al*, 2020[8]	USA	Cohort	2319	10-item self-report tool by Felliti *et al*
10	Schoenaker *et al*, 2019[15]	Australia	Cohort	11 556	10-item self-report tool by Felliti *et al*
11	Miller *et al*, 2017[49]	USA	Prospective study	744	Asked women a series of questions about their family's conditions during childhood
12	Mersky *et al*, 2019[42]	USA	Longitudinal	1848	19-item assessment that has demonstrated good internal consistency
13	Mason *et al*, 2016[35]	USA	Cohort	45 550	Physical abuse and sexual abuse
14	Cammack *et al*, 2018[50]	USA	Cohort	230	Childhood Trauma Questionnaire Short-Form (CTQ)
15	Bala *et al*, 2020[51]	Rhode Island	Population-based survey	3350	7-item questionnaire
16	Ben Salah *et al*, 2019[38]	Tunisia	Prospective follow-up study	593	ACE-International Questionnaire (ACE-IQ)
17	Bhengu *et al*, 2020[39]	South Africa	Cross-sectional	223	WHO-ACE IQ
18	Gillespie *et al*,[52] 2017	USA	Prospective observational design	89	The Stress and Adversity Inventory (STRAIN)
19	Leeners *et al*, 2014[46]	Switzerland	Cohort	225	Using questions modified from a questionnaire developed by Wyatt
20	McDonnell *et al*, 2014[36]	USA	Cohort	398	10-item self-report tool by Felliti *et al*
21	Shaikh *et al*, 2019[40]	Pakistan	Cohort	300	WHO 31-item ACEs
22	Smith *et al*, 2016[53]	USA	Cohort	2303	The main modification of the instrument was to collapse the sexual events before the age of 18 questions into one question asking about childhood sexual abuse before age 18
23	Ranchod *et al*, 2016[54]	USA	Longitudinal study	2873	4-item questionnaire
24	Fredriksen *et al*, 2017[27]	Norway	Cohort	762	10-item self-report tool by Felliti *et al*
25	Hantsoo *et al*, 2019[28]	USA	Observational study	48	10-item self-report tool by Felliti *et al*
26	Howell *et al*, 2019[29]	USA	Observational study	101	10-item self-report tool by Felliti *et al*

Continued

Table 1 Continued

Sl#	First author/pub date	Country	Study design	Sample size	Measurement scale
27	Letourneau *et al*, 2019[30]	Canada	Cohort	907	10-item self-report tool by Felliti *et al*
28	Narayan *et al*, 2018[31]	USA	Cohort	101	10-item self-report tool by Felliti *et al*
29	Racine *et al*, 2020[32]	Canada	Cohort	1994	10-item self-report tool by Felliti *et al*
30	Young-Wolff *et al*, 2019[33]	USA	Cohort	355	10-item self-report tool by Felliti *et al*
31	Barrios *et al*, 2015[41]	USA	Cohort	1521	8 questions from CDC
32	Hardcastle *et al*, 2022[55]	UK	Cross sectional	865	10-item self-report tool by Felliti *et al*

ACE, adverse childhood experience; CDC, Centers for Disease Control and Prevention.

ACEs and risk of pregnancy complications

ACEs and GDM

Six studies[8 15 16 35 36 51] described an association between ACEs and GDM and only one study reported (table 2) there was no association between ACEs and GDM.[42] A large epidemiological study in Australia[15] reported that, in pregnant women, exposure to any three ACEs (adjusted RR (aRR) 1.73, 95% CI 1.0 to 3.0) or four or more ACEs (aRR 1.70, 95% CI 1.00 to 2.90) was associated with elevated GDM risk after adjusting for preconception body mass index, unhealthy diet, parity, and maternal age. Another study in the USA[35] reported that both moderate (adjusted OR (aOR) 1.08, 95% CI 0.96 to 1.22) and severe (aOR 1.42, 95% CI 1.21 to 1.66) childhood physical abuse was associated with an increased risk of GDM. This study also reported that forced sexual activity during childhood was associated with an increased risk of GDM (aOR 1.30, 95% CI 1.14 to 1.49).

ACEs, GWG and HDP

Only one study by Ranchod *et al*[54] examined the association between ACEs and GWG. They found that exposure to physical abuse and household alcohol abuse were independently associated with a 20% increase in the risk of excessive GWG. A study by Stanhope *et al*[8] found that for each ACEs score, there was a slight increase in the HDP risk (aOR 1.03, 95% CI 0.71 to 1.49), although it was not statistically significant. However, they found that physical abuse (aOR 1.22, 95% CI 1.10 to 1.42) and household alcohol abuse (aOR 1.21, 95% CI 1.11 to 1.32) were associated with a significant increase in the risk of excessive GWG (table 2).

ACEs and depression/anxiety

Nine studies[27–33 37 41] examined the association between ACEs and depression/anxiety, with almost all studies reporting a significant positive association during pregnancy(table 2). For example, a large cohort study in Canada[32] reported that ACEs were associated with depressive symptoms in pregnancy (aOR 1.26, 95% CI 1.12 to 1.43). Another study[30] reported that for each maternal ACE, there was an increased risk of symptoms of anxiety and depression during pregnancy. An observational study in the USA by Hantsoo *et al*[28 29] reported that ACEs directly affected depression (B=1.1, SE=0.44, p=0.01).

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

A total of 11 studies (72 889 participants) were available for the quality-effect meta-analysis, which produced an association between maternal any ACEs and risk of any adverse pregnancy complications (OR 1.37, 95% CI 1.20 to 1.57) (figure 2). In risk factor-specific sub-analysis, five studies (7116 participants) were available for meta-analysis, which produced a moderate association between maternal ACEs and risk of GDM (OR 1.39, 95% CI 1.11 to 1.74). For depression/anxiety during pregnancy, four studies (6116 participants) were available for this meta-analysis, which produced an association between maternal ACEs and risk of depression/anxiety during pregnancy (OR 1.5, 95% CI 1.15 to 2.2). Both low (OR 1.30, 95% CI 1.10 to 1.50) and high (OR 1.41, 95% CI 1.02 to 1.90) numbers of ACEs were associated with pregnancy complications (online supplemental figure S1.1 and 1.2).

ACEs and adverse pregnancy outcomes

ACEs and preterm birth

Out of 31 studies, 12[34 38–40 42–48 50 55] reported the association between ACEs and preterm birth (table 3). A study in Tunisia by Ben Salah *et al*[38] 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<0.001) and witnessing community violence (p<0.05). In another study, Harville *et al*[48] reported that violence exposure during childhood was associated with a 44% increased risk of preterm birth (aRR 1.40, 95% CI 1.00 to 1.90). They also found the family mental health issues increased by 24%, and there was a 25% increase in the risk of preterm birth. A case–control study in the USA by Selk *et al*[47] reported that women exposed to forced sex during childhood had a 22% greater risk of preterm birth (aRR 1.2, 95% CI 1.10 to 1.30) than those in the no exposure group. Furthermore, exposure to physical and sexual abuse during childhood was associated with a 35% greater risk of preterm birth (aRR 1.30, 95% CI 1.10 to 1.60). A study by Miller *et al* reported that mothers' childhood economic hardship was independently associated with multiple adverse birth outcomes.[49] A study by Gillespie *et al* reported that maternal childhood abuse

Table 2 Summary of published measures of effect

1	Appleton *et al*, 2019[37]	Depression	ACEs score (continuous)	Pearson's correlation coefficients (0.37)
2	Versteegen *et al*, 2021[16]	GDM	ACEs total	1.05 (0.98 to 1.14)
			ACEs binary	2.85 (1.15 to 7.06)
3	Stanhope *et al*, 2020[8]	GDM	ACEs 4+	1.03 (0.71 to 1.49)
			Continuous ACE score	0.96 (0.88 to 1.04)
		HDP	ACEs 4+	1.03 (0.71 to 1.49)
			Continuous ACE score	1.03 (0.71 to 1.49)
4	Schoenaker *et al*, 2019	GDM	3 ACEs	1.73 (1.02 to 3.01)
			≥4 ACEs	1.76 (1.04 to 2.99)
5	Mason *et al*, 2016[35]	GDM	Mild physical abuse	1.08 (0.96 to 1.22)
			Moderate physical abuse	11.16 (1.04 to 1.29)
			Severe physical abuse	1.42 (1.21 to 1.66).
			Forced sexual activity	1.30 (1.14 to 1.49)
			Combined	1.42 (1.21 to 1.66)
6	Bala *et al*, 2020[51]	GDM	≥3 ACEs	1.24 (0.81 to 1.90)
			1–2 ACEs	1.18 (0.90 to 1.55)
7	McDonnell *et al*, 2014[36]	GDM		GDM not correlated with ACE indicators
8	Ranchod *et al*, 2016[54]	GWG	Physical abuse	1.2 (1.1 to 1.4)
			Household alcohol abuse	1.2 (1.1 to 1.3)
			Household mental illness	1.1 (0.9 to 1.2).
9	Fredriksen *et al*, 2017[15]	Depression	ACEs continuous	1.3 (0.92 to 1.82)
10	Hantsoo *et al*,2019[28]	Depression	<2 ACES	EPDS (median (IQR)): 5 (3–6)
			≥2 ACES	EPDS (median (IQR)): 3 (1.5–6.0)
11	Howell *et al*, 2020[29]	Depression	ACEs continuous	Adverse childhood experiences had a direct effect on depression, B=1.11, SE=0.44, p=0.01
12	Letourneau *et al*, 2019[30]	Depression	ACEs continuous	Maternal ACEs were associated with symptoms of anxiety and depression during pregnancy
13	Narayan *et al*, 2018[31]	Depression	ACEs continuous	Maternal ACEs were associated with depression during pregnancy (β=0.32, p<0.01)
14	Racine *et al*, 2020[32]	Depression	ACEs continuous	1.26 (1.12 to 1.43)
15	Young-Wolff *et al*, 2019[33]	Depression	3+ ACEs	3.08 (1.12 to 7.39)
			1–2 ACEs	2.42 (1.09 to 5.41)
16	Barrios *et al*, 2015[41]	Depression		2.07 (1.58 to 2.71)

ACEs, adverse childhood experiences; EPSD, Edinburgh Postnatal Depression Scale; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HDP, hypertensive disorder of pregnancy.

was associated with birth timing (birth timing was operationalised as a day's gestation at birth continuous variable and calculated according to the obstetric estimate of date of delivery and actual date of delivery extracted from the prenatal and labour and delivery records).[52]

ACEs and low birth weight

Out of 31 studies, six[38 42 44 48 50 53] reported an association between ACEs and low birth weight (table 3).

Harville *et al* reported that violence exposure during childhood was associated with an increased risk of low birth weight (aOR 1.5, 95% CI 1.1 to 2.0). They also found that violence/mental health issues (aOR 1.4, 95% CI 1.1 to 1.9) and issues of family structure increased the risk of low birth weight (aOR 1.4, 95% CI 1.1 to 1.9). A study by Smith *et al* reported that each additional ACE decreased gestational age at birth as well as birth weight.[53]

Meta-analytic results for maternal ACEs and adverse pregnancy outcomes

A total of 12 studies were available for this quality-effects meta-analysis, which produced an association between maternal ACEs and any adverse pregnancy outcomes (OR 1.31, 95% CI 1.17 to 1.47). In a sub-analysis of eight studies (59 607 participants), the quality-effects meta-analysis showed an association between maternal ACEs and preterm birth (OR 1.41, 95% CI 1.16 to 1.71). On the other hand, three studies (7014 participants) were

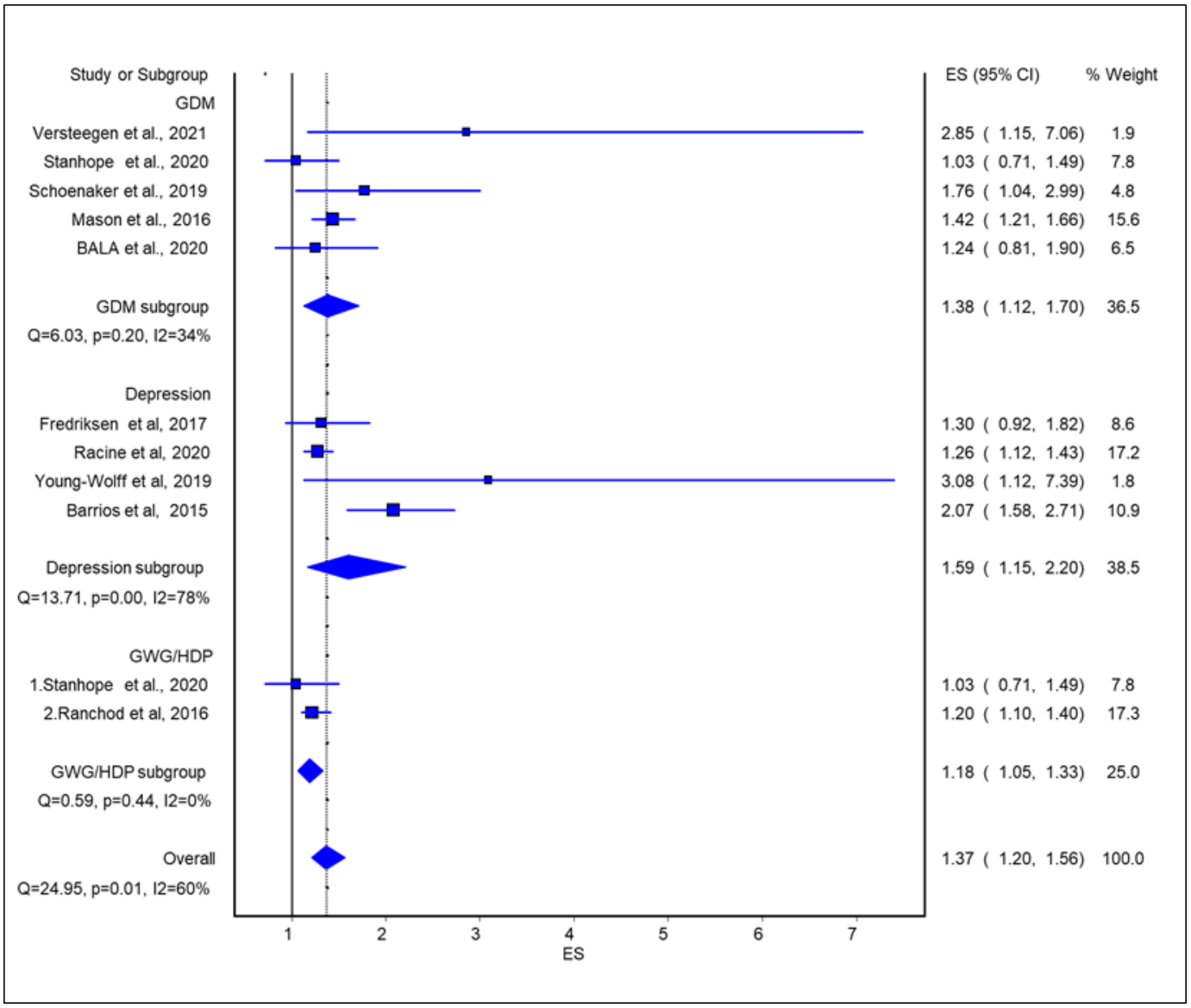

Figure 2 Association of any ACE exposure with risk of pregnancy complications. ACE, adverse childhood experience; ES, effect size; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HDP, hypertensive disorder of pregnancy.

available for the quality-effects meta-analysis for low birth weight, which showed an association between maternal ACEs and low birth weight (OR 1.27, 95% CI 1.17 to 1.47) (figure 3). In low (one to three ACEs) and high (four+) ACEs specific analysis, five studies reported low ACEs exposure and nine studies reported high ACEs exposure. Both low (OR 1.27, 95% CI 1.05 to 1.54) and high (OR 1.41, 95% CI 1.20 to 1.65) ACE exposure showed a significant association with any adverse pregnancy outcome. For each additional unit increase in the number of ACEs, the odds of adverse pregnancy outcomes increased 1.10 times (OR 1.10, 95% CI 1.05 to 1.15) (online supplemental figure S2.1 and 2.2).

DISCUSSION

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

To our knowledge, this is the first systematic review and meta-analysis to assess the association between ACEs and pregnancy complications and adverse pregnancy outcomes. A recent systematic review and meta-analysis

Table 3 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[34]	Preterm birth	High ACE score (≥2 ACE)	2.09 (1.10 to 3.98)
			ACEs score (continuous)	1.18 (0.99 to 1.40)
2	Grimstad *et al*,1999[44]	Preterm birth	Sexual abuse	1.03 (0.44 to 2.4)
		Low birth weight	Sexual abuse	1.21 (0.5 to 2.93)
3	Noll *et al*, 2007[45]	Preterm birth	Sexual abuse	2.16 (0.77 to 6.06)
4	Leeners *et al*, 2014[46]	Preterm birth	Sexual abuse	2.47 (1.11 to 5.51)
5	Selk *et al*, 2016[47]	Preterm birth	Severe physical only	1.02 (0.88 to 0.17)
			Forced sex only	1.22 (1.1 to 1.35)
			Experienced both severe abuse types	1.35 (1.13 to 1.62)
6	Harville *et al*, 2010[48]	Preterm birth	Financial/structural hardship	1.20 (0.90 to 1.60)
			No interest in education	1.17 (0.93 to 1.48)
			Family dysfunction	1.20 (0.94 to 1.52)
			Lack of supportive caregiving	0.98 (0.81 to 1.19)
			Violence/mental health issues	1.24 (0.94 to 1.63)
			Issues of family structure	1.25 (1.02 to 1.54)
			No. of hardships (≥4)	1.45 (1.09 to 1.93)
		Low birth weight	Financial/structural hardship	1.18 (0.88 to 1.60)
			No interest in education	1.18 (0.88 to 1.60)
			Family dysfunction	1.18 (0.88 to 1.60)
			Lack of supportive caregiving	1.18 (0.88 to 1.60)
			Violence/mental health issues	1.48 (1.12 to 1.96)
			Issues of family structure	1.48 (1.12 to 1.96)
			No. of hardships (≥4)	1.48 (1.12 to 1.96)
11	Miller *et al*, 2017[49]	Birth outcomes	Childhood economic hardship	Mother's hardship independently associated with multiple adverse birth outcomes
12	Mersky *et al*, 2019[42]	Preterm birth	ACE scores (continuous)	1.07 (1.01 to 1.12)
			1 or 2 ACEs	1.22 (0.79 to 1.89)
			3 or 4 ACEs	1.29 (0.82 to 2.02)
			5 or more ACEs	1.46 (0.95 to 2.26)
		Low birth weight	ACE scores (continuous)	1.08 (1.03 to 1.15)
			1 or 2 ACEs	0.98 (0.62 to 1.56)
			3 or 4 ACEs	1.22 (0.76 to 1.96)
			5 or more ACEs	1.39 (0.88 to 2.19)
		Pregnancy loss	ACE scores (continuous)	1.12 (1.08 to 1.17)
			1 or 2 ACEs	0.93 (0.66 to 1.31)
			3 or 4 ACEs	1.27 (0.89 to 1.80)
			5 or more ACEs	1.27 (0.89 to 1.80)
14	Cammack *et al*, 2018[50]	Low birth weight	Emotional abuse	0.88 (0.66 to 1.00) Cohen's kappas (95% CI)
			Physical abuse	0.50 (0.01 to 0.99)
			Sexual abuse	0.75 (0.43 to 1.00)
			Emotional neglect	0.59 (0.18 to 1.00)
			Physical neglect	0.28 (–0.16 to 0.73)

Continued

Table 3 Continued

SI#	First author/pub date	Outcomes	Types of ACEs and analytical unit	Findings (OR, 95% CI)
		Preterm birth	Emotional abuse	0.78 (0.55 to 1.00)
			Physical abuse	0.69 (0.36 to 1.00)
			Sexual abuse	0.78 (0.55 to 1.00)
			Emotional neglect	0.44 (0.12 to 0.77)
			Physical neglect	0.39 (–0.03 to 0.81)
		NICU admission	Emotional abuse	0.58 (0.25 to 0.91)
			Physical abuse	0.28 (–0.15 to 0.71)
			Sexual abuse	0.73 (0.45 to 1.00)
			Emotional neglect	0.55 (0.20 to 0.90)
			Physical neglect	0.55 (0.20 to 0.90)
16	Ben Salah *et al*, 2019[38]	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[39]	Preterm birth	ACEs continuous	1.21 (1.03 to 1.43)
18	Gillespie *et al*. 2017[52]	Birth timing	ACEs continuous	Cumulative childhood stress predicted birth timing (p=0.01)
19	Leeners *et al*, 2014[46]	Preterm birth		CSA, physical abuse as well as other ACEs were associated with an increased risk for premature delivery
21	Shaikh *et al*, 2019[40]	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[55]	Preterm birth	1 ACE	0.80 (0.32 to 2.00)
			2–3 ACEs	1.17 (0.46 to 2.97)
			≥4 ACEs	2.67 (1.14 to 6.23)

ACEs, adverse childhood experiences; CSA, child sexual abuse; NICU, neonatal intensive care unit.

reported an association between ACEs and maternal depression and/or anxiety in the perinatal period (pregnancy to 1 year postpartum),[22] though the results of our study are not directly comparable to this study because outcomes were considered at different perinatal windows and results were presented differently (eg, effect size vs OR). Our results on maternal ACEs and increased risk of adverse pregnancy outcomes are more comprehensive than previous systematic reviews[18 56 57] due to the availability of 12 recent primary studies. Overall, the direction and strength of the associations in our study are similar to these earlier studies.[18 56 57]

There could be several potential direct and indirect pathways to explain the relationship between ACEs and pregnancy complications and adverse pregnancy outcomes. Direct mechanisms may include altering the regulation of stress-signalling pathways[58] and immune system function[59]; changing brain structure and function; and changing the expression of DNA and by accelerating cellular ageing.[60] For example, abuse or neglect might directly lead to malnutrition. Similarly, stress can directly lead to dysregulation of the hypothalamic-pituitary-adrenal axis and associated neuroendocrine-immune[61] as well as epigenetic effects.[62] Results from animal models[63 64] and longitudinal human studies such as the Nurses' Health Study[35] have proposed that a strong history of ACEs may alter the hypothalamic-pituitary-adrenal axis as reflected by elevated cortisol levels that in turn alter glucose metabolism and body weight regulation. Brain development begins in fetal life and continues into early adulthood. Early life maternal ACEs may alter the structure and function of the brain.[65 66] These neurodevelopmental alterations may result in neuroendocrine disruption of cortisol regulation, linked to glucose metabolism.[67 68] The experience of ACEs increased the risk of physical or sexual abuse during pregnancy and is associated with placental damage, uterine contractions, premature rupture of membranes, and genitourinary infections which ultimately increase the risk of preterm birth and low birth weight.[69] Exposure to ACEs is also

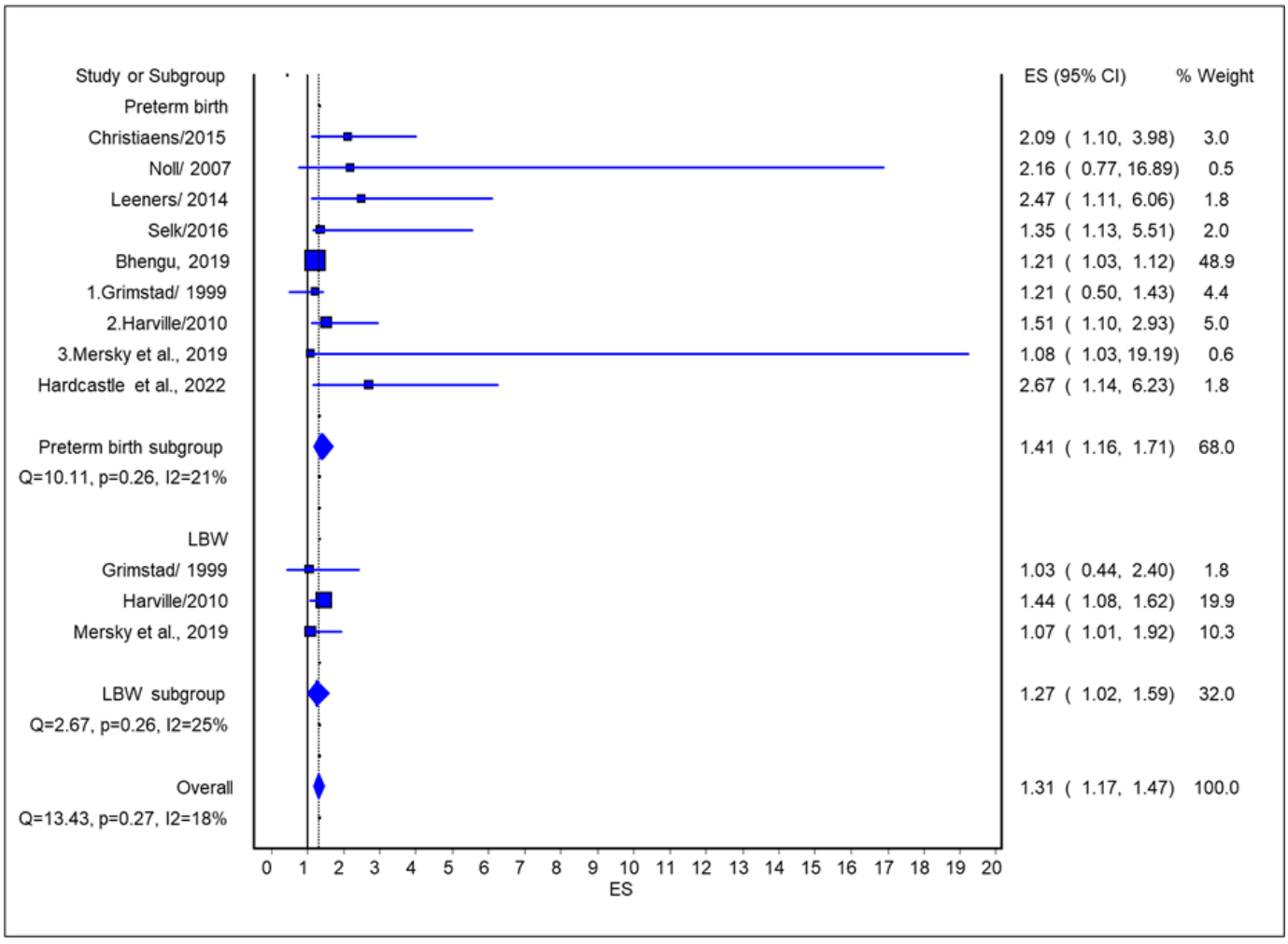

Figure 3 Association of any ACE exposure and adverse pregnancy outcomes. ACE, adverse childhood experience; ES, ???; LBW, low birth weight.

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.[70] In addition, it is also established that socioeconomic status and cumulative disadvantage produces health disparities across the life course.[71] 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.[72 73] The interplay of these different pathways remains largely unclear.

According to our findings and other systematic review evidence, it may be valuable to assess the role of routine ACEs screening during pregnancy to improve maternal and child health. Trauma-informed care is not well incorporated into clinical practice guidelines. Much of the emphasis in maternity care is on individual behaviour change, including advice about diet, exercise, smoking cessation and uptake of clinical care. Approaches that do not incorporate the personal experiences of trauma by women attending antenatal services may inadvertently cause iatrogenic harm. For many years, there has been an interest in improving pregnancy outcomes by focusing on a limited set of physical parameters that can easily be measured such as gestational weight gain, without attention to the underlying mechanisms.[74 75] Overall, studies of diet and exercise in pregnancy to reduce GDM, HDP and other adverse pregnancy outcomes have been disappointing.[76]

A recent scoping review by Tran *et al*[77] found that healthcare providers perceive that they are not being trained to screen for ACEs in their undergraduate training programme or in their professional training in clinical settings. In addition, healthcare workers already have a high demand on their time and limited capacity to incorporate new practices without additional resources. There is some controversy about whether screening for ACEs is a safe and ethical practice, especially if the consequences of discussing ACEs (eg, effects on mental health) cannot be readily addressed.[78 79] These identified barriers are similar to those reported by healthcare providers in relation to ACE screening in general clinical settings.[80] Healthcare providers may appreciate the

importance of asking about ACEs to help raise issues that otherwise would be unknown and unaddressed.[77] Furthermore, Mishra *et al*[81] found that ACEs screening did not excessively disrupt clinic workflow. and was both acceptable for the patient and feasible for the provider. However, to determine if screening for ACEs is worthwhile, studies need to assess whether trauma-informed clinical care translates to improved clinical outcomes for mother and offspring.[82] Beyond screening for ACEs, our findings emphasise the importance of preventing ACEs in children to reduce immediate impacts as well as intergenerational transmission of ACEs. As well as supporting clinicians and providing services to address ACEs, there is growing awareness of the crucial role of upstream policy- and community-level interventions to improve and support positive family and social environments and a need for wide-scale testing of the effectiveness of such interventions.[83 84]

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

Conclusion

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

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