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## Total Adverse Childhood Experiences and Preterm Birth: A Systematic Review

--Manuscript Draft--

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<b>Abstract:</b>	<p><b>Introduction:</b> Total adverse childhood experiences (ACEs) are gaining prominence as a risk factor for preterm birth (PTB). The emerging literature examining this relationship reports inconsistent findings. The purpose of this systematic review was to summarize the available evidence exploring whether total ACEs predict PTB.</p> <p><b>Methods:</b> A total of 386 studies were returned from searches on PubMed, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Nine studies were selected for final analysis and synthesis based on reporting of total ACEs and preterm birth gestational weeks or standard definition of birth before 37 weeks' gestational age. A systematic review rather than meta-analysis was selected to present the findings given the clinical and methodological (e.g., sample studied, measurement tools) heterogeneity of the retrieved studies and pregnancy outcomes measured.</p> <p><b>Results:</b> The nine studies report on birth outcomes for 6,087 women from a range of sociodemographic and ethnic backgrounds. Despite a wide range of study designs, measurement tools, and timings of ACE exposure across studies, seven of the nine included studies showed significant relationships between ACEs and PTB.</p> <p><b>Conclusion:</b> Systematic review of the literature suggests that total ACEs are associated with PTB and provides an overview on the known associations. However, to date only nine studies have assessed this link, and more studies are needed, to explore the associations between ACEs and PTB using appropriate and valid instruments and doing so among more diverse populations. Future research should also explore possible biological mechanisms (allostatic load), and moderating and mediating variables.</p>	

## Title Page

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# **Total Adverse Childhood Experiences and Preterm Birth: A Systematic Review**

## **Abstract**

### **Introduction**

Total adverse childhood experiences (ACEs) are gaining prominence as a risk factor for preterm birth (PTB). The emerging literature examining this relationship reports inconsistent findings. The purpose of this systematic review was to summarize the available evidence exploring whether total ACEs predict PTB.

### **Methods**

A total of 386 studies were returned from searches on PubMed, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Nine studies were selected for final analysis and synthesis based on reporting of total ACEs and preterm birth gestational weeks or standard definition of birth before 37 weeks' gestational age. A systematic review rather than meta-analysis was selected to present the findings given the clinical and methodological (e.g., sample studied, measurement tools) heterogeneity of the retrieved studies and pregnancy outcomes measured.

### **Results**

The nine studies report on birth outcomes for 6,087 women from a range of sociodemographic and ethnic backgrounds. Despite a wide range of study designs, measurement tools, and timings of ACE exposure across studies, seven of the nine included studies showed significant relationships between ACEs and PTB.

### **Conclusion**

Systematic review of the literature suggests that total ACEs are associated with PTB and provides an overview on the known associations. However, to date only nine studies have

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4 25 assessed this link, and more studies are needed, to explore the associations between ACEs and  
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6 26 PTB using appropriate and valid instruments and doing so among more diverse populations.  
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9 27 Future research should also explore possible biological mechanisms (allostatic load), and  
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11 28 moderating and mediating variables.  
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### 16 30 **Keywords**

18  
19 31 adverse childhood experiences, preterm birth, childhood maltreatment, childhood household  
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21 32 dysfunction  
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### 26 34 **Significance**

28  
29 35 *What is already known on this subject?* Adverse childhood experiences which includes  
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31 36 various forms of negative, stressful and traumatic events that occur in early childhood can impact  
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33 37 health and wellbeing across the lifespan. *What this study adds?* Our systematic review suggests  
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36 38 that total ACEs are associated with PTB despite a wide range of study designs, measurement  
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38 39 tools, and timings of ACE exposure across the seven of the nine studies showing a positive  
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41 40 relationship.  
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### 46 42 **Introduction**

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48 43 An estimated 15 million infants each year are born before thirty-seven weeks' gestational  
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50 44 age (GA; WHO 2018) and are considered to be born preterm. Preterm birth (PTB) is associated  
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52 45 with increased rates of morbidity, mortality, and long-term neurodevelopmental impairment  
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55 46 (Ramachandrappa and Jain 2009; Ray et al. 2017), and these infants have significantly higher  
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58 47 rates of neonatal mortality compared with term infants (22.9 per 1,000 PTB versus 0.6 per 1,000  
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4 48 term births) (Ray et al. 2017). Given the high prevalence of neonatal morbidity and mortality  
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6 49 among PTB infants, preventing PTB remains a global priority (WHO 2012; WHO 2018).  
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9 50 Although maternal health before and during pregnancy is recognized as essential to birth  
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11 51 outcomes, less is known about the exact causes and etiology of PTB (Dean et al. 2013). Maternal  
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13 52 stress, distress, and many biopsychosocial processes occurring throughout women's lives,  
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15 53 including throughout women's pregnancies, are thought to play significant roles and have  
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17 54 multiplicative effects in the causal pathways to PTB, particularly for women living in low- and  
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19 55 middle-income (LMI) countries (Premji et al. 2015; Wadhwa et al. 2011). The  
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21 56 psychobiobehavioural model characterizes the interplay of individual stress reactivity,  
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23 57 maladaptive patterns of biological responses because of wear and tear from acute and chronic  
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25 58 stress-related physiological response over time (i.e., allostatic load), and maladaptive health  
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27 59 behaviors (e.g., smoking, drinking) in the multisystem pathway to PTB (Premji et al. 2015).  
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33 60 Adverse childhood experiences (ACEs) are defined as traumatic experiences occurring  
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35 61 prior to the age of eighteen (Felitti et al. 1998). Early definitions of ACEs have expanded over  
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37 62 the past two decades and now include multiple types of early life trauma, categorized as:  
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39 63 childhood maltreatment (i.e., sexual abuse, physical abuse, emotional abuse, physical neglect,  
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41 64 and emotional neglect), household dysfunction (i.e., household substance use, partial separation  
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43 65 or divorce, family member imprisonment, family member with mental illness, and domestic  
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45 66 violence) and three additional stressful experiences [bullying, witnessing community violence,  
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47 67 and collective violence (witnessing war)] for a total of thirteen ACE indicators (Felitti et al.  
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49 68 1998; WHO 2014). ACEs have been shown to have long-term and intergenerational  
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51 69 consequences on both maternal health, and child health and behavioral outcomes (Gray et al.  
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53 70 2017; Madigan et al. 2017; McDonald et al. 2019).  
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4 71 Abuse, both as an individual ACE and as a condition of maternal health directly before  
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6 72 and during pregnancy, is well-studied as a predictor of PTB (see Hillis et al. 2004; Nesari et al.  
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9 73 2018; Selk et al. 2016). In a meta-analysis of fourteen moderate-to-high quality studies, maternal  
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11 74 history of abuse at any time-point before pregnancy, including during childhood, was found to be  
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14 75 associated with PTB (OR= 1.28, 95% CI=1.12-1.47) (Nesari et al. 2018). While the meta-  
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16 76 analysis found connections between prior maternal experiences of abuse (an individual ACE)  
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19 77 and PTB (Nesari et al. 2018) of unquestionable importance, it is also the case that ACEs co-  
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21 78 occur in children’s lives. Felitti et al. (1998) conducted the foundational study demonstrating the  
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24 79 importance of the combined effects of ACEs (total ACEs) on health outcomes. A few studies  
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26 80 have begun to study the association between maternal total ACEs and PTB (Ben Salah et al.  
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29 81 2019; Christiaens et al. 2015; Dickerson 2017; Leeners et al. 2014; McDonnell and Valentino  
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31 82 2016; Shaikh et al. 2020; Smith et al. 2016), and therefore, the purpose of this systematic review  
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34 83 was to compile and critically synthesize this literature guided by the following question: What is  
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36 84 the association between total ACEs and preterm birth?

## 85 **Methods**

### 86 **Search Strategy and Study Selection**

87 Three databases [PubMed, PsychINFO, and Cumulative Index to Nursing and Allied  
88 Health Literature (CINAHL)] were searched using keywords that included the following four  
89 terms: (a) “premature birth”; (b) “infant, premature” (in PubMed, CINAHL) or “premature  
90 infant” (PsycINFO); (c) “preterm birth”; and (d) “birth outcome”. Two of the terms (a and b)  
91 were listed as major search terms (Medical Subject Heading or MeSH in PubMed, major subject  
92 or mjsub in PsycINFO, and CINAHL heading word or MW in CINAHL) whereas the other two  
93 (c and d) were entered without this specification. These search terms were combined with the

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4 94 search terms "adverse childhood experiences", "childhood trauma", "child abuse", and "child  
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6 95 neglect" entered as regular search terms and the term "violence" entered as a major search term  
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9 96 (see Appendix 1 for exact search box and results for each database). The final search was  
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12 97 conducted in November 2020.

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14 98 Only studies assessing total ACEs were considered, and studies reporting on single ACEs  
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16 99 were excluded. ACEs was measured retrospectively in all studies while pregnancy was either  
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19 100 followed prospectively or retrospectively. Studies were excluded if the outcome of interest was  
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21 101 low birth weight which is reflective not only of prematurity but also of poor fetal growth  
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23 102 resulting from maternal, fetal or placental health. Only studies published in English were  
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26 103 considered given lack of resources (language expertise and translation costs) and time.

#### 27 28 104 **Data Extraction**

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31 105 From each of the nine selected studies, information was pulled together in a summary  
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33 106 matrix table to highlight similarities and differences between studies (Table 1). Criteria included:  
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36 107 year, author, country, participant demographics, study design, sample size, study methods  
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38 108 (instrument), timing of data analysis, and findings related to PTB (i.e., odds ratio, confidence  
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41 109 intervals, and p-values). Countries were classified based on income level. World Bank defines  
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43 110 high-income countries as those with a gross national income (GNI) per capita of \$12,536USD or  
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46 111 more, upper middle-income countries as those with GNI per capita between \$4,046USD and  
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48 112 \$12,535USD and low-income countries as those with a GNI per capita of US\$1,035USD or less  
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51 113 in 2019 (World Bank, 2021).

#### 52 53 114 **Study Quality and Bias**

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55 115 This study used a methodological quality checklist tool similar to the one developed by  
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58 116 Shah (2010) and adapted by Staneva et al. (2015), a tool specifically designed for the assessment  
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117 **Table 1**118 **Characteristics of Included Studies**

Author (year)	Country	Sample Description	Study Design	Sample size	Instrument	Time of measure of ACEs	Findings
Ben Salah et al. (2019)	Tunisia (LMI)	From Primary Health Care Centers; Region of Monastir (Tunisia); Avg age 29.1yr	Prospective longitudinal cohort study with exposure to violence assessed retrospectively using ACEs	593 women	Arabic version WHO ACE-IQ adapted for Tunisian context, version validated in Saudi Arabia; ACEs divided into intra-familial and social ACEs (i.e., peer violence, witnessing community violence, & exposure to war/collective violence	Within second trimester	Prematurity more prevalent among women with social ACEs history (P<0.0001). Gestational weeks reduced in presence of: peer violence [unadjusted] ( $\beta$ =-0.39; 95% CI: -0.69, -0.09, P < 0.01); collective violence [unadjusted] ( $\beta$ =-1.42; 95% CI: -1.9, -0.94, P < 0.001); collective violence [adjusted] ( $\beta$ =-1.15; 95% CI: -1.69, -0.62, P < 0.001) and witnessing community violence [adjusted] ( $\beta$ =0.42; 95% CI: 0.07, 0.77, P < 0.05). Relationship between total ACEs and pregnancy outcome mediated by depression
Bhengu et al. (2019)	South Africa (Upper middle-income)	From public sector district hospital; mostly Black African (92.4%); Avg age 27.7yr (all women enrolled)	Comparative cross-sectional study with retrospective reporting of ACEs	223 women (118 HIV negative, 105 HIV positive)	WHO ACE-IQ, using in-person interviews	Within first week postpartum	Mean ACE score (binary) of 3.28 (SD=2.76) and PTB rate of 8.97% (all participants). Greater ACE score was significantly associated with PTB birth (aOR=1.20; 95% CI: 1.02, 1.42) (all participants). When adjusted by HIV status, the odds of preterm birth were lower for HIV negative status



Author (year)	Country	Sample Description	Study Design	Sample size	Instrument	Time of measure of ACEs	Findings
							(aOR=0.04; 95% CI=0.01, 0.19) and HIV positive suppressed viral load (aOR=0.06, 95% CI: 0.01, 0.24) when compared to HIV unsuppressed status.
Christiaens et al. (2015)	Canada (High-income)	From three hospitals in Edmonton, mostly Caucasian (84% of cases; 83% of controls); Avg age 28.3yr (cases); 29.6yr (controls)	Case-Control (Retrospective)  Mothers who delivered term and mothers who delivered preterm infants.	622 women (412 controls and 210 cases) recruited; 223 women (75 cases and 148 controls) in analysis (call rate 35%)	Wellbeing and pregnancy questionnaire (a grouping of checklists and validated research instruments including ACE score (Felitti et al. 1998)	Postnatal time period (3-months to 1-year)	High ACE score of 2+ ACEs significantly associated with increased PTB risk (aOR 2.09, 95% CI: 1.10, 3.98; P=0.024).
Gillespie et al. (2017)	USA (born and raised; High-income)	From obstetrics and gynecology clinics in two hospitals and community around Columbus, Ohio. African American, non-Hispanic; Avg age 26.5yr; primarily low SES	Prospective observational design	96 pregnant women (89 in analysis)	STRAIN (96 acute and chronic stressors); blood cortisol; days gestation at birth	28 – 32 6/7 weeks' GA	Cumulative childhood stress predicted birth timing (P=0.01): interpersonal loss (ab=0.02, 95% CI: 0.001, 0.045); physical danger (ab=0.02 95% CI: 0.001, 0.043); cortisol biological mediator. Note: stress in adulthood was controlled
Leeners et al. (2014)	Germany (High-income)	CSA group recruited from "Frauennotruf" support centers and control group recruited from local kindergartens, gynecological offices, or dental	Case-control (Retrospective)  Sexually abused women and comparison group	375 (132 CSA and 243 comparison without CSA) recruited; 255 women (85 exposed to CSA and 170 comparison	CSA explored using questionnaire (Wyatt 1985); ACE explored through interview questions	Anytime during study period of 18 months (several years after birth)	Women who delivered PTB infants at greater likelihood of past exposure to either CSA (P=0.0239), physical abuse (P=0.0223) or other ACEs (P=0.0093)

Author (year)	Country	Sample Description	Study Design	Sample size	Instrument	Time of measure of ACEs	Findings
		offices. Nearly all Caucasian (98.8% in cohort; 99.4% in comparison); Avg age 26.6yr (cases); 27.5yr (controls)		without CSA <sup>8</sup> ) in analysis			
McDonnell and Valentino (2016)	USA (High-income)	From local Women, Infants, and Children (WIC) offices located in a medium-sized Midwestern city; 53.3% Caucasian; 30.4% African American; 16.3% Other; Avg age 24.76yr	Prospective longitudinal	398 pregnant women recruited; 315 birth outcomes	FHHQ (commonly used in high-risk, low-income groups)	Prenatal time period (within 4.84 months (SD=2.14) of due date)	GA not correlated with ACE indicators
Mersky and Lee (2019)	USA (High-income)	Low income (98% ≤ 200% of federal poverty line/federal means-tested benefits; federal Maternal Infant & Early Childhood Home Visiting Program; 41.1% Caucasian; 24% African American; 23.2% Hispanic; Avg age 25.5yr	Secondary analysis of longitudinal study	1848 women (1823 in analysis)	Childhood Experiences Survey (19-item with 10 indicators summed for total ACE)	Within 90 days of starting home visiting program.	Total ACE score associated with PTB (OR=1.07; 95% CI: 1.01, 1.12; P<0.01) while controlling for maternal age, race/ethnicity, and education

Author (year)	Country	Sample Description	Study Design	Sample size	Instrument	Time of measure of ACEs	Findings
Shaikh et al. (2020)	Pakistan (LMI)	From four secondary hospital – 3 in Karachi, and one in Hyderabad; 29.6% Muhajir; 19.7% Sindhi, 15.2% Memon, 35.3% Other; Avg age 26.8yr	Secondary analysis of prospective longitudinal cohort study	300 women recruited; 263 birth outcomes	WHO ACE-IQ	12-19 weeks' GA	Mean PTB rate of 11.1% (95% CI: 7.7%, 15.4%). ACE-IQ (binary and frequency score) not significantly associated with PTB.
Smith et al. (2016)	USA (High-income)	From 137 obstetrical practices/hospital-based clinics around Connecticut and Western Massachusetts; 76% Caucasian; 17% Hispanic/other; Avg age 31yr	Prospective cohort	6438 (1905 eligible with depression and randomly selected 1612 of 4533 without depression); 2303 pregnant women (included women with and without depression)	ETI-SF (a shortened version of ETI-SR, a validated tool)	During second interview which was at 28(±2) weeks' GA	Direct effect: each unit increase of ACE was associated with a decrease in 0.063 weeks' GA (accounting for race/ethnicity). Indirect effect: each unit of ACE increase was associated with a decrease of 0.041 weeks (adjusted) (95% CI: -0.070, -0.018). Smoking accounted for most of the differential effect

*Note:* yr: year; ACE: Adverse Childhood Experiences; WHO: World Health Organization; IQ: International Questionnaire; CI: confidence interval;  $\beta$ : beta coefficient; HIV: human immunodeficiency virus; SD: standard deviation; PTB: preterm birth; aOR: adjusted odds ratio; USA: United States of America; SES: socio-economic status; STRAIN: Stress and Adversity Inventory; GA: gestational age; ab: indirect effect; CSA: childhood sexual abuse; FHHQ: Family Health History Questionnaire; ETI-SF: Early Trauma Inventory-Self-report Short Form; ETI-SR: Early Trauma Inventory-Self-report.

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4 124 of quality and bias in studies exploring PTB and low birth weight as outcomes. Each single study  
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6 125 was assessed against six categories—selection, exposure assessment, outcome assessment,  
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9 126 confounding factor, analytical, and attrition—with preset definitions on which to determine bias  
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11 127 as none, low, moderate or high detailed elsewhere (Shah 2010; Staneva 2015). Individual studies  
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14 128 were given a score for each criteria that ranged from ‘none’ (no bias), ‘little’, ‘moderate’, and  
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16 129 ‘high’/‘cannot tell’ (extensive bias) (Shah 2010; Staneva et al. 2015). A final bias score for each  
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19 130 study was calculated based on the score that was seen most frequently across the six areas of  
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21 131 assessment for each study.

## 23 132 **Study design**

26 133         Although a meta-analytic review was originally considered, studies were not suitable for  
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29 134 combination due to the diversity of individual study designs, sample characteristics, and the  
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31 135 various screening tools used across the single studies. A systematic review of the literature was  
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33 136 ultimately selected to look collectively at studies, comment methodologically on the quality of  
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36 137 available studies, and to highlight participant demographics (e.g. geographies, ethnicities, ages)  
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38 138 in which the outcome of interest (PTB) was, or was not, found (Ryan 2013). The narrative  
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41 139 review also allowed for a comparison of studies, exploring whether similar or dissimilar  
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43 140 intermediate outcomes and known confounders (for example, smoking) were assessed across  
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46 141 individual study designs (Ryan 2013).

## 48 142 **Results**

### 50 143 **Study Selection**

53 144         The search strategy yielded 287 studies in PubMed, 75 studies in PsycINFO, and 111  
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55 145 studies in CINAHL, resulting in 386 studies after removal of 87 duplicate and triplicate records  
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58 146 (see Fig. 1). Non-human animal studies were considered beyond the scope of this manuscript. In  
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5 147 an initial step, the title and abstract of each article were screened, and 335 articles were excluded  
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7 148 because they were clearly irrelevant.  
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10 149 A full-text review of 51 articles by two independent reviewers was undertaken against  
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12 150 predetermined inclusion and exclusion criteria (Fig. 1). Discrepancies and uncertainties about  
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14 151 whether studies met the inclusion criteria were discussed between two reviewers, and consensus  
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17 152 was reached. Of the 51 articles, 42 were excluded because they had no or no adequate measure  
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19 153 of total ACEs, two studies because PTB was treated as the predictor variable of offspring total  
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21 154 ACEs, two because low birth weight, not PTB, was the outcome, one because menarche and the  
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24 155 contribution of age of menarche to birth outcomes was studied, and two manuscripts because  
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26 156 they were systematic or meta-analytic reviews.  
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## 28 29 157 **Description of Studies**

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31 158 Birth outcomes for 6,087 individual women were studied across the nine studies (Table  
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33  
34 159 1). Two studies (Ben Salah et al. 2019; Shaikh et al. 2020) were conducted in the LMI country of  
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36 160 Pakistan (Shaikh et al. 2020) and another in Tunisia (Ben Salah et al. 2019). Seven studies were  
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39 161 conducted in high or upper-middle income countries, including four studies from the USA  
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41 162 (Gillespie et al. 2017; McDonnell and Valentino 2016; Mersky and Lee 2019; Smith et al. 2016),  
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44 163 one study from Canada (Christiaens et al. 2015), one study from Germany (Leeners et al. 2014),  
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46 164 and one study from South Africa (Bhengu et al. 2019).  
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48  
49 165 Recruitment settings and procedures, and the nature of study designs varied across  
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51 166 studies. Participants were recruited from primary health care centers (Ben Salah et al. 2019),  
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53 167 hospitals (Bhengu et al. 2019; Christiaens et al. 2015), or offices of federal programs for high-  
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55  
56 168 risk women such as Women, Infants, and Children (McDonnell and Valentino 2016), and a  
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58 169 Maternal Infant and Early Childhood Home Visiting Program (Mersky and Lee 2019). Study  
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4 170 samples varied widely between 89 African-American women in a small, prospective study  
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6 171 (Gillespie et al. 2017) to a large, prospective cohort study of 2,303 mostly Caucasian women  
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8 172 (Smith et al. 2016). All were observational studies but varied in the temporal nature of the study  
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11 173 designs: five studies used prospective designs with women being assessed for ACEs during  
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13 174 pregnancy and followed for pregnancy outcome (Ben Salah et al. 2019; Bhengu et al. 2019;  
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15 175 Gillespie et al. 2017; McDonnell and Valentino 2016; Shaikh et al. 2020; Smith et al. 2016) and  
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18 176 two studies used retrospective designs (Christiaens et al. 2015; Leeners et al. 2014). Two studies  
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21 177 conducted secondary analysis of a longitudinal study (Mersky and Lee 2019; Shaikh et al. 2020).  
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23 178 The studies utilized varied types of design, including cohort (Ben Salah et al. 2019; Gillespie et  
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25 179 al. 2017; McDonnell and Valentino 2016; Mersky and Lee 2019; Shaikh et al. 2020; Smith et al.  
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27 180 2016), comparative cross-sectional (Bhengu et al. 2019) and case-control (Christiaens et al.  
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29 181 2015; Leeners et al. 2014).  
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33 182         The majority of studies included women of varying ethnicities. In five studies, women  
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35 183 were predominantly Caucasian (Christiaens et al. 2015; Leeners et al. 2014; McDonnell and  
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37 184 Valentino 2016; Mersky and Lee 2019; Smith et al. 2016). The other three studies (Bhengu et al.  
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39 185 2019; Gillespie et al. 2017; Shaikh et al. 2020) included participants with a diverse range of  
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41 186 ethnicities, including one study in which nearly all women were Black African (Bhengu et al.  
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43 187 2019), in another study (Shaikh et al. 2020) women were Pakistani with various ethnicities  
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45 188 (Muhajir, Sindhi, Memon, or other), while in another study women were African American, born  
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47 189 and raised in the USA (Gillespie et al. 2017). The Tunisian study (Ben Salah et al. 2019) did not  
48  
49 190 describe the ethnic origins of the participants. All studies employed purposive or convenience  
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51 191 sampling. All study data was collected in clinical-type settings, or over the phone. The  
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53 192 pregnancy outcome of weeks' or days' GA was collected from pre-existing data, medical records  
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193 (e.g., prenatal and labor and delivery forms) or from interviews with women and checked against  
 194 medical chart data. Studies that categorized pregnancy outcome by type of delivery (i.e., preterm  
 195 birth or term birth) used the standard definition of less than 37 weeks' GA.

## 196 **Study Quality and Bias**

197 Seven studies (Ben Salah et al. 2019; Bhengu et al. 2019; Christiaens et al. 2015;  
 198 Gillespie et al. 2017; Leeners et al. 2014; Shaikh et al. 2020; Smith et al. 2016) were assessed as  
 199 having no or low bias overall notwithstanding high selection bias (Gillespie et al. 2017),  
 200 moderate risk of analysis bias (Bhengu et al. 2019; Gillespie et al. 2017), and moderate attrition  
 201 bias (Christiaens et al. 2015; Leeners et al. 2014; Smith et al. 2016). Two studies (McDonnell  
 202 and Valentino 2016; Mersky and Lee 2019) were assessed as having moderate overall bias based  
 203 on the high selection bias (Mersky and Lee 2019), attrition bias (McDonnell and Valentino  
 204 2016), moderate risk of bias in outcome assessment (Mersky and Lee 2019), and our inability to  
 205 tell whether the study had risk of bias in analysis and controlled appropriately for confounding  
 206 factors (McDonnell and Valentino 2016) (Table 2).

## 208 **Table 2**

209 **Risk of bias** (Shah 2010; Staneva et al. 2015)

210 Studies	211 Selection	212 Exposure assessment	213 Outcome assessment	214 Confounding factor	215 Analytical	216 Attrition	217 Overall bias assessment
218 Ben Salah et al. (2019)	219 None	220 None	221 None	222 Low	223 Low	224 None	225 None
226 Bhengu et al. (2019)	227 Low	228 Low	229 None	230 None	231 Moderate	232 None	233 Low
234 Christiaens et al. (2015)	235 None	236 Low	237 None	238 None	239 None	240 Moderate	241 None
242 Gillespie et al. (2017)	243 High	244 None	245 None	246 None	247 Moderate	248 Low	249 Low

Leeners et al. (2014)	None	None	None	None	None	Moderate	None
McDonnell and Valentino (2016)	None	Low	None	Cannot tell	Cannot tell	High	Moderate
Mersky and Lee (2019)	High	Low	Moderate	None	Low	None	Moderate
Shaikh et al. (2020)	None	None	None	None	Low	Low	None
Smith et al. (2016)	None	Low	None	None	None	Moderate	None

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### 211 **Exposure Assessment: ACEs**

212 The nine studies each collected information about total ACEs at various times during  
213 prenatal or postpartum period and used various measurement tools (see Table 1 for details). Five  
214 studies measured ACEs during pregnancy (Ben Salah et al. 2019; Gillespie et al. 2017;  
215 McDonnell and Valentino 2016; Shaikh et al. 2020; Smith et al. 2016), one study explored ACEs  
216 and PTB at the same time within the first week postpartum (Bhengu et al. 2019), and three  
217 studies assessed ACEs at various times in the postpartum period (Christiaens et al. 2015; Leeners  
218 et al. 2014; Mersky and Lee 2019) and did not always specify the exact time (Mersky and Lee  
219 2019). Of note, the Wellbeing and Pregnancy Questionnaire (Christiaens et al. 2015) used the  
220 10-items from the original ACE study (Felitti et al. 1998), the WHO ACE-IQ (Ben Salah et al.  
221 2019; Bhengu et al. 2019; Shaikh et al. 2020), which is intended for use in all countries, was  
222 recently validated for use in Nigeria, a lower middle-income country (Kazeem 2015) and  
223 Malawi, a low-income country (Kidman et al. 2019) and the FHHQ (McDonnell and Valentino  
224 2016) has been previously validated for use with low-income high-risk populations. Most studies  
225 controlled for known confounding factors of PTB, including maternal smoking and alcohol use  
226 in pregnancy. Notably, Bhengu et al. (2019) adjusted for socio-economic status, finding no



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4 227 change to ACE totals when adjusted, while Gillespie et al. (2017) controlled for stress in  
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7 228 adulthood, finding that stress occurring in childhood predicted birth timing. Some studies also  
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9 229 examined mediators (direct/indirect) of the relationship between ACE and preterm birth  
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12 230 including depression (Ben Salah et al. 2019), race/ethnicity (Smith et al. 2016), and cortisol  
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14 231 (Gillespie et al. 2017).

### 232 **Outcome Measurement: Preterm birth**

19 233 All nine studies examined the association between total ACEs and the pregnancy  
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21 234 outcome of PTB, and just two (McDonnell and Valentino 2016; Shaikh et al. 2020) showed no  
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24 235 significant association. Two studies (Christiaens et al. 2015; Smith et al. 2016) reported  
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26 236 decreases in GA with increasing exposure to the number of ACEs. In the prospective cohort  
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29 237 study by Smith et al. (2016), for each unit increase in ACE, GA decreased by 0.063 weeks when  
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31 238 accounting for race/ethnicity and 0.041 weeks (corrected for bias) when considering indirect  
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34 239 effects through mediators, with smoking accounting for just under half of the effect. Similarly, in  
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36 240 their case-controlled study, Christiaens et al. (2015) found that for every additional ACE, the risk  
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38 241 of PTB increased by eighteen percent (aOR 1.18; 95% CI: 0.99, 1.40). Moreover, women with  
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41 242 two or more ACEs had a two-fold increased risk of PTB (aOR 2.09; 95% CI: 1.10, 3.98;  
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43 243 P=0.024) (Christiaens et al. 2015). These studies highlight the importance of cumulative ACE  
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45  
46 244 exposure in increasing PTB risk. Mersky and Lee (2019), while controlling for maternal age,  
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48 245 race/ethnicity, and education, found the total ACE score was associated with PTB (OR=1.07;  
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51 246 95% CI: 1.01, 1.12; P<0.01). In a cross-sectional study, Bhengu et al. (2019) found that greater  
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53 247 ACE scores were significantly associated with PTB (aOR=1.20; 95% CI 1.02-1.42). However,  
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55 248 the odds of preterm birth were lower for HIV-negative women when adjusted for HIV status (see  
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58 249 Table 1).

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4 250 Leeners et al. (2014) also found that childhood sexual abuse, itself an ACE, was  
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6 251 associated with an increased risk for premature delivery compared to an unexposed group  
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9 252 (18.8% compared to 8.2%,  $P=0.024$ ). PTB was also more likely to occur in women who had  
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11 253 experienced other ACEs (e.g., emotional abuse, substance abuse in family members, mentally  
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13 254 handicapped family members, family members at risk for suicide, and family members in prison)  
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16 255 ( $P=0.009$ ) or physical abuse in childhood ( $P=0.022$ ) (Leeners et al. 2014, p. 173). While  
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19 256 controlling for stress in adulthood, Gillespie et al. (2017) noted that childhood stress, specifically  
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21 257 interpersonal loss ( $ab = 0.02$ , 95% CI: 0.001, 0.045) and physical danger ( $ab = 0.02$  95% CI:  
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23 258 0.001, 0.043) predicted birth timing with cortisol serving as a biological mediator.

26 259 In contrast to these associations, McDonnell and Valentino (2016) found no correlation  
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28 260 between ACE indicators (childhood household maltreatment and childhood household  
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30 261 dysfunction) and GA in women, in a majority never-married and racially diverse sample of  
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32 262 women, recruited from local Women, Infants, and Children offices located in a Midwestern city  
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34 263 in the USA. Moreover, McDonnell and Valentino (2016) found no significant differences  
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36 264 between infant GA and several predictor variables (i.e., age of first pregnancy, infant birth  
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38 265 weight, child 6-month Ages and Stages Questionnaire (ASQ) score, and Beck Depression  
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40 266 Inventory scores). The authors of that study note that based on these findings of non-  
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42 267 significance, they did not consider any further analysis of GA (McDonnell and Valentino 2016).  
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44 268 Similarly, Shaikh et al. (2020) found no association between ACE and preterm birth using both  
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46 269 the binary and frequency score of the ACE-IQ.

## 53 270 **Discussion and Conclusion**

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55 271 The intent of this systematic review was to provide an overview of the associations  
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57 272 between maternal total ACEs and PTB, based in the current research literature. While our initial  
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4 273 goal was to conduct a meta-analytic review, the nine studies we identified could not be combined  
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6 274 meaningfully due to the heterogeneity of the sample characteristics, inclusion and exclusion  
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9 275 criteria, timing of the exposure measurement, and measurement tools. Three studies (Gillespie et  
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12 276 al. 2017; McDonnell and Valentino 2016; Mersky and Lee 2019) recruited women with very  
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14 277 specific characteristics (see Table 1) and were thus not comparable to women in the other  
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16 278 studies. Substantial variability existed in the participant demographics across studies, including  
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19 279 variability in the proportions of races and ethnicities, education levels, employment status,  
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21 280 marital status, parity, illicit drug use, and age. Bhengu et al. (2019) enrolled mostly Black South  
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24 281 African women (92.4%) who were single, divorced or widowed, while Shaikh enrolled Pakistani  
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26 282 low-risk women (i.e., no high-risk health or obstetric complications) who were married, and Ben  
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29 283 Salah at al. (2019) enrolled Tunisian who also had high-risk pregnancies (i.e., had diabetes or  
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31 284 high blood pressure). Only Bhengu et al. (2019) and Shaikh et al. (2020) included family or  
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33 285 household income. Two of the studies excluded participants with histories of PTBs, multifetal  
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36 286 pregnancies, and complications during pregnancy from the control group (Smith et al. 2016;  
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38 287 Christiaens et al. 2015). Smith et al. (2016) recruited pregnant women who used antidepressant  
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41 288 medication, experienced symptoms of trauma (i.e., general trauma and physical, emotional and  
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43 289 sexual abuse) or post-traumatic stress, or were clinically diagnosed as depressed, alongside a  
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46 290 healthy comparison group; whereas, McDonnell and Valentino (2016) recruited pregnant women  
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48 291 and followed them until after six months postpartum, irrespective of their depression status. In  
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51 292 contrast, Christiaens et al. (2015) and Bhengu et al. (2019) recruited postpartum women who had  
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53 293 delivered term and preterm infants. Lastly, Leeners et al. (2014) recruited participants who had  
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55 294 delivered a live baby anytime in past five years, who were not currently pregnant, and who had a  
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4 295 history of sexual abuse, alongside a healthy comparison group, with the age at first delivery and  
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6 296 number of children matched between groups.  
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9 297 While the studies employed diverse methods and strategies to study ACEs and PTB,  
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11 298 overall, the findings from seven of the nine studies identified suggest an increased risk for PTB  
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13 299 when women were exposed to ACEs. Two studies (McDonnell and Valentino 2016; Shaikh et al.  
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15 300 2020) did not and it is possible that the specific limitations in the study (McDonnell and  
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17 301 Valentino 2016) or socio-cultural context (Shaikh et al. 2020) may explain differences in  
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19 302 findings. McDonnell and Valentino (2016) report high attrition rates in their study which may  
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21 303 misrepresent the actual occurrence of PTB and warrants further consideration. Of the many risk  
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23 304 factors for PTB, some risk factors have been considered as mediators between ACEs and  
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25 305 pregnancy outcomes, for example, smoking, history of a psychiatric disorder, and substance use  
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27 306 (Smith et al. 2016). Whereas the majority of the studies in this review considered many of these  
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29 307 risk factors, McDonnell and Valentino (2016) did not do so to the same degree, limiting the  
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31 308 possible analyses and interpretations of the roles and extent of PTB mediators in that study.  
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33 309 Shaikh et al. (2020) used a different tool (ACE-IQ: binary and frequency scores) to measure  
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35 310 ACEs when compared to studies that showed an association (e.g., Christiaens et al., 2015; Smith  
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37 311 et al., 2016). A low report of ACEs was evident among Pakistani women enrolled in the study by  
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39 312 Shaikh et al. (2020) and neither the number of ACEs nor ongoing exposure to ACEs was  
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41 313 associated with preterm birth. The appraisal of ACEs and the lack of impact of ACEs on  
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43 314 pregnancy outcomes (i.e., reactivity to stress) may have been influenced by shared or acceptable  
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45 315 sociocultural norms, and environmental context of the women who resided in a LMI country  
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47 316 (Bright et al. 2018; Shaikh et al. 2020).  
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4 317 Most studies did not explore in great detail the mechanism of action and biopsychosocial  
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6 318 pathways whereby ACEs are believed to influence health outcomes. A notable exception is a  
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9 319 study by Gillespie et al. (2017) who explored a stress-related biological pathway whereby  
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11 320 indirect effects of childhood stress on birth timing were estimated by maternal cortisol level.  
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14 321 Their secondary analyses were guided by the “placental clock” theory in which cumulative  
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16 322 childhood stress alters the hypothalamic-pituitary-adrenal (HPA) reactivity leading to rapid rise  
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19 323 in cortisol which when detected by the fetal/placental unit alters the rate of production of  
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21 324 placental corticotropin-releasing hormone which controls the timing of birth (Gillespie et al.  
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24 325 2017). The biopsychosocial pathways whereby ACEs are believed to influence pregnancy  
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26 326 outcome such as preterm birth is a promising area of research. For example, several studies have  
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29 327 explored the effects of allostatic load, a measure of the combined effects of physiological stress,  
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31 328 and how, over time (with advanced age), accumulated allostatic load can affect the body’s  
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34 329 normal regulation mechanisms (Chyu and Upchurch 2011; Ribeiro et al. 2018), including birth  
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36 330 outcomes (Wallace and Harville 2013). In our systematic review, although McDonnell and  
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38 331 Valentino (2016) did not find an association between PTB and ACEs, their study sample  
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41 332 represented the youngest average participant age of the nine studies, suggesting this sample of  
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43 333 younger women may have experienced less accumulation of allostatic load which potentially  
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46 334 could have offered some age-related protection against PTB outcomes.  
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48 335 Allostatic load biomarkers have been studied across various sociodemographic categories  
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50 336 to demonstrate the physiological effects arising out of social living conditions (i.e., education and  
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53 337 racialization) (Chyu and Upchurch 2011; Geronimus et al. 2006). For example, in a large US  
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55 338 national survey, Chyu and Upchurch (2011) found greater allostatic load scores and faster  
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58 339 allostatic load accumulation (by age) among black women compared to white or Mexican  
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4 340 women. Moreover, Chyu and Upchurch (2011) found that women with lower family income  
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6 341 levels, and women with only a high school education, had higher mean allostatic load scores.  
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9 342 Looking specifically at allostatic measures and PTB, Wallace and Harville (2013) explored PTB  
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11 343 among white and Black women in the United States, finding that across both races GA decreased  
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14 344 as allostatic load increased.

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16 345 It should be noted seven of the nine studies included in this synthesis were conducted in  
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19 346 high and upper-middle income countries and the majority of participants were Caucasian. As  
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21 347 evidence mounts showing disparities among more socially-disadvantaged women (and  
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24 348 connections to biological markers) there will be a need for future research exploring the possible  
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26 349 connections between ACEs and PTB to include diversely-situated women, including women of  
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29 350 diverse races, ethnicities, and socio-economic classes. Some of the studies included here  
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31 351 exemplify the integration of local context in studying ACEs and PTB outcome, for example: a  
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33 352 high HIV endemic area with concerns about adherence to anti-retroviral therapy, and substance  
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36 353 use (Bhengu et al. 2019); low-income women enrolled in a federal Maternal Infant & Early  
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38 354 Childhood Home Visiting Program (Mersky and Lee, 2019); and more recently, women  
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41 355 specifically from specific regions in LMIC, including the region of Monastir, Tunisia (Ben Salah  
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43 356 et al. 2019) and cities of Karachi and Hyderabad, Pakistan (Shaikh et al. 2020). Still, we argue  
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46 357 there is a need for additional contextualized primary studies in LMI countries where PTB is  
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48 358 known to have especially high incidence rates (Premji et al. 2015; Shaikh et al. 2020). To more  
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51 359 fully understand the longstanding and far-reaching health effects of ACEs globally, more  
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53 360 research using the ACE-IQ scale in middle and particularly in low-income countries is needed  
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56 361 (Kidman et al. 2019; World Health Organization 2009/2011). Such scholarship could build on  
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4 362 recent research that has newly validated the use of ACE-IQ tool in populations in Nigeria and  
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6 363 Malawi, respectively (Kazeem 2015; Kidman et al. 2019).  
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9 364 **Limitations**

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11 365 This systematic review is limited insofar as there have been few studies on total ACEs  
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14 366 and PTB from which to draw. In our comprehensive search, we retrieved only nine studies that  
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16 367 matched our search criteria. It remains a possibility that studies that reinforce the null hypothesis  
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19 368 of no association between ACEs and PTB, may be less often published than studies showing a  
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21 369 positive relationship (Joobar et al. 2012). This possibility may partially explain why we found  
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24 370 only two studies that did not show a relationship between ACEs and PTB. In addition, we found  
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26 371 only two recently published studies conducted on the relationship between ACEs and PTB in  
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29 372 LMI countries, suggesting that much of the wider global health implications of ACEs on PTB are  
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31 373 still to be studied. Our systematic review also relied on English-language studies thus may not  
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33 374 represent all of the studies in the field thus introducing risk of bias.  
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36 375 A limitation across all of the primary studies looking at childhood experiences through  
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38 376 ACE indicators, and therefore also our review, is the strong measurement bias of ACE as data  
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41 377 was collected retrospectively (i.e., recall bias), the possibility of participant self-reporting bias,  
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43 378 and social desirability bias (Althubaiti 2016). Similarly, disease status of the sample, for  
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46 379 example, participants screened for ACEs while experiencing depression, may have influenced  
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48 380 the degree to which women reported ACEs (Wright et al. 2012). Nonetheless, the use of  
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51 381 validated screening tools employed in each of the primary studies likely decreased such risks  
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53 382 (Althubaiti 2016).  
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55 383 Moreover, while the included primary studies touched on the negative health trajectories  
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58 384 often seen with ACEs, we found limited discussion of measures that might prevent ACEs and  
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4 385 PTB outcomes. Social support, for example, has been studied as a promising mediator of many  
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6 386 of the pregnancy risks associated with ACEs (Racine et al. 2018). More studies are needed, to  
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9 387 explore the associations between ACEs and PTB including the possible biological mechanisms  
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11 388 (allostatic load), and moderating and mediating variables.  
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### 13 389 **Conclusion and Implications**

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16 390 The results of this narrative synthesis summarize the current literature exploring  
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19 391 connections between ACEs and PTB with seven of the nine studies included in our review  
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21 392 demonstrating connections between these measures. However, further research is needed to  
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24 393 explore the associations between ACEs and PTB using appropriate and valid instruments and  
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26 394 doing so among more diverse populations. Moreover, it will be necessary to explore the  
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29 395 associations between ACEs and PTB alongside ongoing research about allostatic load and the  
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31 396 mechanisms related to how the body is able to remember traumatic early childhood events and  
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33 397 how exactly these phenomena can lead to adverse adult outcomes. Future research should also  
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36 398 explore possible moderating and mediating variables in the pathway linking ACEs to PTB.  
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399 **Fig. 1**

400 Comprehensive search strategy and inclusion of studies in the narrative synthesis using the

401 PRISMA model (Moher et al. 2009)

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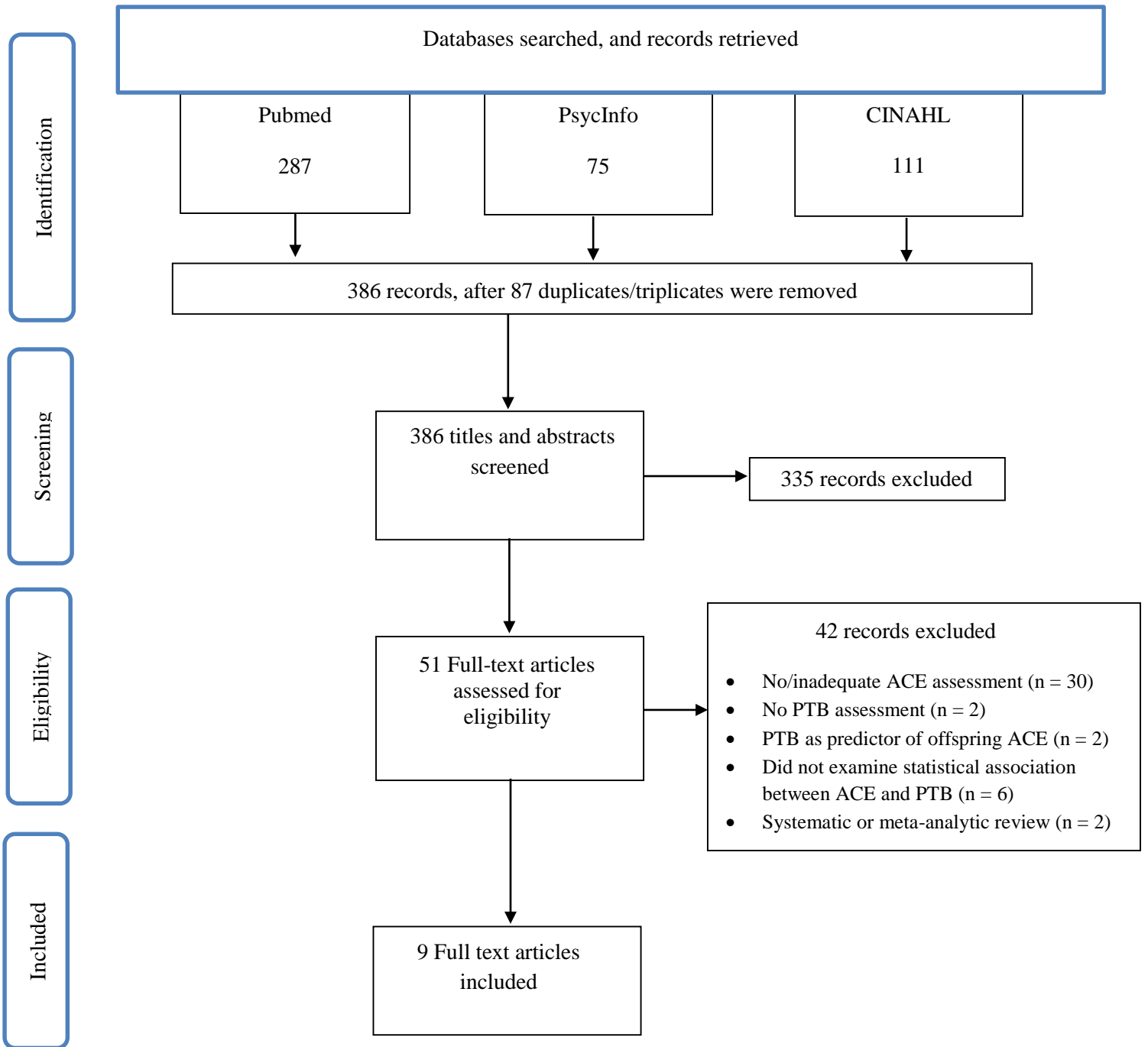
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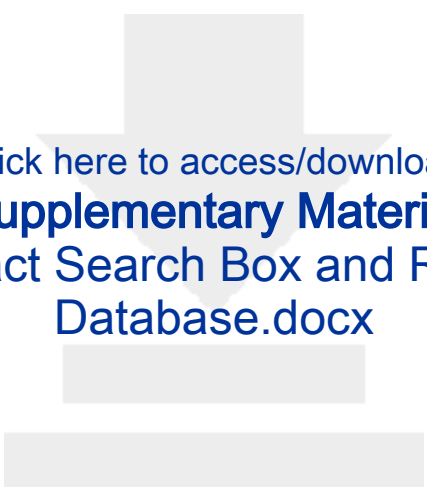
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Fig. 1 Flowchart





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**Supplementary Material**

Appendix 1 Exact Search Box and Results for Each  
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