2-3-2020

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Journal of Affective Disorders 267 (2020) 49–56

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Ethnic disparity and exposure to supplements rather than adverse childhood experiences linked to preterm birth in Pakistani women

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ARTICLE INFO

Keywords:
Ethnic disparity
Adverse childhood experiences
Preterm birth
Supplements
Depression
Anxiety

ABSTRACT

Background: Adverse childhood experiences (ACEs) are associated with prenatal mental health and negative pregnancy outcomes in high income countries, but whether the same association exists in Pakistan, a low- to middle-income (LMI) country, remains unclear.

Methods: Secondary data analyses of a prospective longitudinal cohort study examining biopsychosocial measures of 300 pregnant women at four sites in Karachi, Pakistan. A predictive multiple logistic regression model for preterm birth (PTB; i.e., <37 weeks' gestation) was developed from variables significantly ($P < 0.05$) or marginally ($P < 0.10$) associated with PTB in the bivariate analyses.

Results: Of the 300 women, 263 (88%) returned for delivery and were included in the current analyses. The PTB rate was 11.1%. We found no association between ACE and PTB. Mother's education ($P = 0.011$), mother's ethnicity ($P = 0.010$), medications during pregnancy ($P = 0.006$), age at birth of first child or current age if primiparous ($P = 0.049$) and age at marriage ($P = 0.091$) emerged as significant in bivariate analyses. Mother's ethnicity and taking medications remained predictive of PTB in the multivariate model.

Limitations: Findings are limited by the relatively small sample size which precludes direct testing for possible interactive effects.

Conclusions: In sum, pathways to PTB for women in LMI countries may differ from those observed in high-income countries and may need to be modelled differently to include behavioural response to emotional distress and socio-cultural contexts.

1. Introduction

Preterm birth (PTB; i.e., birth <37 completed weeks) is a global health concern affecting 15 million babies every year (World Health Organization, 2018a). Low- and middle-income (LMI) countries, like Pakistan, experience a higher burden of PTB (World Health Organization, 2018a). PTB may be stress-induced with emerging models exploring the impact of stressors that reoccur over the course of the lifespan (i.e., adverse childhood experiences or ACEs) on maternal mental health during pregnancy and pregnancy outcomes (Wadhwa et al., 2011; Atzi et al., 2019). The cumulative physiologic burden of systemic wear and tear on the body from adaptations to these reoccurring stressors may explain the differences in rates of PTB McEwen and Wingfield, 2003(). Risk factors for PTB for women in LMI countries have not been fully explored nevertheless likely include complex interactions between multiple factors (e.g., demographic, socio-economic, ACEs, maternal mental health, behaviour) (Premji and MiGHT, 2014).

ACEs including traumatic experiences such as abuse, neglect, household dysfunction resulting from alcohol or other substance use,

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https://doi.org/10.1016/j.jad.2020.01.180
Received 20 September 2019; Received in revised form 18 November 2019; Accepted 31 January 2020
Available online 03 February 2020

and violence (Felitti et al., 1998; World Health Organization, 2018b) can impact maternal physical and emotional health during pregnancy and pregnancy outcomes (Smith et al., 2016; Sun et al., 2017). Literature from high-income countries demonstrates that a dose-response relationship exists between ACEs and increased PTB risk (Christiaens et al., 2015; Smith et al., 2016). After taking race/ethnicity into consideration, for every single ACE (Christiaens et al., 2015) or unit of ACE (Smith et al., 2016) the chances of PTB increased by roughly 18% (Christiaens et al., 2015) or gestational age decreased by 0.063 weeks (Smith et al., 2016).

Women from South Asian countries like Pakistan frequently experience severe forms of familial, social, and neighbourhood stress (Fisher et al., 2011; Premji et al., 2015). socio-economic adversity including poverty, gender discrimination, and conflict (i.e., neighbourhood) contribute to conditions that increase the likelihood of ACEs (Biglan et al., 2017). The ACEs that are most related to health conditions include interpersonal violence, and mental illness (Hughes et al., 2017). Based on the Pakistan Demographic and Health Survey 2017–2018, the prevalence of intimate partner violence was 34% (National Institute for Population Studies (NIPS) [Pakistan] and ICF, 2019). Norms that define gender roles and acceptability of domestic violence not only contribute to high rates of intimate partner violence but also prenatal maternal anxiety (Bright et al., 2018). Similarly, antenatal depression, a common maternal health disorder, has a prevalence rate of 25.3% (Gelaye et al., 2016) compared to 7–13% in high-income countries (Bennett et al., 2004). Findings from our earlier pilot study (Shaikh et al., 2011) on less affluent Pakistani women in Karachi showed high rates of self-reported antenatal depression (41%) and antenatal stress (20%) with the odds of PTB 1.44 times higher in women with depression than women without depression (Shaikh et al., 2011). Studies from high-income countries have reported inconsistent findings, with a minority of the studies (Dayan et al., 2002; Jesse et al., 2003; Orr et al., 2002) finding a statistically significant association between antenatal depression and PTB with a small effect size (Dunkel Schetter and Tanner, 2012; Grote et al., 2010). In our systematic review and meta-analysis examining maternal anxiety and PTB, heterogeneity was reduced when restricting the predictor variable to state anxiety and pregnancy-related anxiety (which includes fears and worries about self, fetus, ability to care for the infant, and health care delivery) (Rini et al., 1999; Rose et al., 2016).

To the best of our knowledge this is the first study to examine the influence of ACEs on maternal mental health and pregnancy outcome for women residing in LMI countries, specifically, Karachi, Pakistan. An approach to care that considers the social, economic, and cultural environments provides perspectives on broader public health strategies (Afulani et al., 2017), and has the potential to improve the emotional and physical health of pregnant women and reduce risk of adverse pregnancy outcomes as a consequence of ACEs (Phillips et al., 2016).

2. Methods

2.1. Study design

We completed secondary analysis of data from a prospective cohort study examining patterns of psychosocial and biological responses across the continuum of pregnancy. Recruitment occurred at four centres – Hyderabad, Garden, Kharadar and Karimabad – of the Aga Khan Hospital for Women and Children in Karachi, Pakistan. Data were collected from pregnant women at 12–19 weeks' gestation and 22–29 weeks' gestation. Birth outcome data were obtained from medical records and postnatal wards of the four centres. Pregnancies were dated using last menstrual period, the most consistent method available for all women.

2.2. Study procedures

Pregnant women were recruited between October 2015 and July 2016, if they met the following criteria: (a) 18 years and older, (b) singleton pregnancy, (c) 12–19 weeks' gestation, (d) willing to return for assessment 10 weeks later (i.e., 22–29 weeks gestation), (e) able to speak Urdu or English, and (f) planning to deliver at the same location.

Women were excluded if they were (a) unable to give informed consent; (b) experiencing high-risk health or obstetric complications (e.g., chronic renal, heart disease, or psychotropic drug use); or (c) experiencing major health problems known to affect neuroendocrine or immune function (e.g., HIV/AIDS). Women with self-reported co-morbidities such as gestational hypertension and diabetes were included as these were hypothesized to result from stress related multisystem dysregulation in the pathway to PTB (Premji and MiGHT, 2014). The Ethical Review Committee of Aga Khan University (ID: 3564-SON-ERC-15) and Conjoint Health Research Ethics Board of University of Calgary approved the study (ID: REB15-2372).

2.3. Instruments

We used the World Health Organization 31-item ACEs – International Questionnaire (ACE-IQ) (World Health Organization, 2018b), which is intended to be completed by adults 18 years and older in any country, to assesses adverse childhood experiences including family dysfunction; physical, sexual and emotional abuse and neglect by parents or caregivers; peer violence; and exposure to community violence (i.e., witnessed) and collective violence (World Health Organization, 2018b). The 10-item Perceived Stress (PS) 5-point Likert scale (Cronbach's alpha = 0.78-0.91), available in the Urdu language (http://www.psy.cmu.edu/~schohen/scales.html), determined the degree to which specific events in the past month were viewed as stressful (Cohen et al., 1983; Cohen & the Psychosocial Working Group, 2000). Appropriate items were reverse scored and summed to generate PS scores ranging between 0 and 40 (Cohen et al., 1983; Cohen & the Psychosocial Working Group, 2000). The 10-item Pregnancy-Related Anxiety (PRA) revised 4-point Likert scale (Rini et al., 1999) evaluated each woman's feelings related to her health during pregnancy, the health of fetus/infant, and her labour and delivery. Where appropriate items were reverse scored and summed to generate a PRA score (10–40) (Rini et al., 1999). The 10-item Edinburgh Perinatal Depression Scale (EPDS) (Cronbach's alpha = 0.73–0.87; 3 to 12 weeks test-retest coefficient = 0.53–0.074; split-half reliability = 0.73–0.83) measured depressive symptoms in pregnancy with scores ranging between 0 and 30 (Bergink et al., 2011; Cox et al., 1987; Murray and John, 1990). Each of these instruments was administered at enrolment and a self-report questionnaire elicited data on potential covariates – demographic factors, behavioural factors, pre-pregnancy characteristics, pregnancy characteristics, and socio-cultural factors (Denton et al., 2004). The PS, PRA, and EPDS were re-administered at follow up 10 weeks later.

2.4. Statistical methods

Using WHO guidelines (World Health Organization, 2018b), 13 indicators of ACE-IQ were defined from the 31-items and a single score of ACE-IQ, from 0 to 13, was obtained for binary (i.e., affirmative response) and frequency (i.e., occurrence of event - once, a few times or many times) (World Health Organization, 2018b) methods of analysis (Table 1). For the other instruments (PS, PRA, and EPDS) aggregate scores were obtained.

Of the 300 pregnant women enrolled in the study, 263 (88%) returned for delivery and were included in the analysis. Data for all three time points was available for 249 (83%) women. The overall PTB rate was 11.1% (95% CI: 7.7%, 15.4%). We used Agresti and Brent (1998) method to estimate percentages and 95% confidence intervals of each

Table 1
Number of pregnant women (out of 263) with ACE and estimated percentage with 95% confidence interval (Blencowe et al., 2012).

Sno	ACE-IQ Item	ACE Indicator Type	Number of pregnant women with ACE (n = 263)	Estimated % of pregnant women with ACE	Estimated 95% CI Lower	Upper
5	Parent died or divorce	Common	56	21.7	16.8	26.7
1	Alcohol or drug abuse in household	Common	16	6.7	3.7	9.7
3	Mentally ill household member	Common	11	4.8	2.3	7.4
2	Incarcerated household member	Common	3	1.8	0.2	3.5
4	Contact sexual abuse	Common	3	1.8	0.2	3.5
6	Emotional neglect	Binary	46	18.0	13.4	22.6
12	Community Violence	Binary	44	17.2	12.7	21.7
8	Household member treated violently	Binary	37	14.6	10.4	18.8
9	Emotional Abuse	Binary	22	9.0	5.5	12.4
7	Physical Neglect	Binary	11	4.8	2.3	7.4
10	Physical abuse	Binary	6	3.0	0.9	5.0
11	Bullied	Binary	4	2.2	0.5	4.0
13	Collective Violence	Binary	0	0.7	0.0	1.7
8	Household member treated violently	Frequency	17	7.1	4.0	10.2
6	Emotional neglect	Frequency	8	3.7	1.4	6.0
12	Community Violence	Frequency	7	3.3	1.2	5.5
7	Physical Neglect	Frequency	4	2.2	0.5	4.0
9	Emotional Abuse	Frequency	4	2.2	0.5	4.0
10	Physical abuse	Frequency	1	1.1	0.0	2.3
11	Bullied	Frequency	1	1.1	0.0	2.3
13	Collective Violence	Frequency	0	0.7	0.0	1.7

ACE = adverse childhood experience; ACE-IQ = adverse childhood experience – international questionnaire; % = percentage; CI = confidence interval; Sno = serial number on the ACE-IQ; shaded items do not belong to ACE survey developed in the US (Felitii et al., 1998).
Note: "Common" items were scored in the affirmative (yes or no) for both the binary and frequency method of analysis to obtain a score ranging from 0 to 13.

type of ACE given the small cell frequencies. Since less than a quarter of pregnant women had a score of two or more on binary or frequency ACE-IQ score, we categorized ACEs into 3-groups – no ACEs, one ACE and 2 or more ACEs – for all subsequent analysis. Moreover, since the frequency of occurrence of each traumatic event was limited with estimated percentages 10% or less, only data for the ACE-IQ binary (referred to as ACE) are presented and augmented with data for ACE-IQ frequency where appropriate (referred to as ACE frequency).

Bivariate associations were examined using percentages and Fisher's exact test and the likelihood ratio test. We used one-way analysis of variance to investigate if the mean of the quantitative variables differed among the 3 categories (0, 1, and 2 +) of each of the ACE-IQ methods of analysis (binary versus frequency). When a significant difference was found, we performed post-hoc analysis to determine which pairs of categories (0 and 1; 0 and 2 + ; and 1 and 2 +) of the ACE-IQ binary or frequency differed significantly. Independent sample T-test enabled comparison between mean current age, age at first marriage, age at first birth, as well as PS, PRA, and EPDS scores among women with PTB and those without PTB. We investigated homogeneity of variances with Levenes test (Brown & Forsythe, 1974). If a statistically significant relationship between a demographic or other variable and PTB, and between that variable and the ACE-IQ score emerged, we examined the potential for interaction between the variable and ACE-IQ in predicting PTB. Interactions were conservatively considered statistically significant at $P < 0.10$. We developed a predictive multiple logistic regression model for PTB with these variables and interactions, using the forward likelihood criterion to arrive at a parsimonious predictive model.

3. Results

3.1. ACE

The most frequent ACE was "parent died or divorced," with an estimated 21.7% (95% CI: 16.8 to 26.7%) of women afflicted (Table 1). None of the women reported experiencing collective violence. Among the remaining items, the most frequent traumatic experiences were emotional neglect (18.0%; CI 13.4 to 22.6%), community violence (17.2%; CI 12.7 to 21.7%) and household member treated violently (14.6%; CI 10.4 to 18.8%).

3.2. Association of ACE-IQ and socio-demographic/psychosocial factors

The aggregate ACE scores ranged from 0 to 9 with 126 (47.9%), 78 (29.7%) and 59 (22.4%) of pregnant women having none, one, and 2 or more ACEs, respectively. Location of recruitment ($P < 0.001$), mother's ethnic group ($P = 0.022$), consenting to the choice of husband ($P = 0.014$) and taking medications during pregnancy ($P < 0.001$) were associated with ACEs (Tables 2a and 2b). The majority of pregnant women at Garden (58.0%) and Hyderabad (61.8%) reported no ACEs at all, and a smaller number at Garden (13.2%) and Hyderabad (14%) reported two or more ACEs. By contrast, 55.9% of women at Kharadar and 27.9% at Karimabad reported two or more ACEs.

The majority of Sindhi women (63.5%) and Memon women (62.5%) had no ACEs, compared to approximately 40% of women from minority ethnic groups (i.e., other). In addition, Sindhi women were less likely to report 2 or more ACEs than other women. The majority (53.8%) of the 173 women in arranged marriage reported no ACEs compared to just 36.7% of the 90 women that had a choice. However, similar percentages of women who reported a choice (23.3%) and those who did not (22.1%) reported 2 or more ACEs. Most of the women taking "medications" were taking supplements, notably folic acid, multi-vitamins, Osnate-D (for calcium and Vitamin D deficiency in pregnancy), Ca-C 1000 Calvive (for low levels of Vitamin C) and Fefol vit (iron, vitamins, and folic acid). The only notable medication was Duphaston which was taken by 11.7% of the 145 women who took medications. Many women taking medication reported no ACEs (57.9%) and few (15.2%) experienced two or more ACEs. The only socio-demographic variable associated with ACE (frequency) was ethnicity ($P = 0.048$).

Although the mean PRA score increased with the number of ACEs, the increases are not large enough to be statistically significant ($P = 0.326$) (Table 3). Post-hoc analysis revealed that for women without ACEs had significantly lower EPDS scores than women with one ($P < 0.001$) or those with two or more ACEs ($P < 0.001$). A

Table 2a
Relationship between ACE-IQ binary categorical and socio-demographic factors.

		n	ACE-IQ binary categories			*P*-value
			0	1	>=2	
			n (%)	n (%)	n (%)	
Location	Garden	100	58 (58.0%)	28 (28.3%)	14 (14.0%)	<0.001
	Hyderabad	68	42 (61.8%)	17 (25.0%)	9 (13.2%)	
	Karimabad	61	21 (34.4%)	23 (37.7%)	17 (27.9%)	
	Kharadar	34	5 (14.7%)	10 (29.4%)	19 (55.9%)	
Father's Education	No Formal School/Primary School	72	36 (50.0%)	21 (29.2%)	15 (20.8%)	0.086
	High School Completed	60	22 (36.7%)	19 (31.7%)	19 (31.7%)	
	Attended or Completed Post-Secondary Studies	74	45 (60.8%)	19 (25.7%)	10 (13.5%)	
	Attended or Completed Graduate Studies	57	23 (40.4%)	19 (33.3%)	15 (26.3%)	
Mother's Education	No Formal School/Primary School	65	32 (49.2%)	20 (30.8%)	13 (20.0%)	0.996
	Secondary or High School completed	59	27 (45.8%)	18 (30.5%)	14 (23.7%)	
	Attended or Completed Post-Secondary Studies	92	43 (46.7%)	27 (29.3%)	22 (23.9%)	
	Attended or Completed Graduate Studies	139	67 (48.2%)	40 (28.8%)	32 (23.0%)	
Household Income	<Rs 10,000	37	18 (48.6%)	12 (32.4%)	7 (18.9%)	0.235
	Rs 10,001–20,000	62	28 (45.2%)	18 (29.0%)	16 (25.8%)	
	Rs 20,001–40,000	83	34 (41.0%)	24 (28.9%)	25 (30.1%)	
	>Rs 40,000	70	37 (52.9%)	22 (31.4%)	11 (15.7%)	
	Not Known*	11	9 (81.8%)	2 (18.2%)	0 (0.0%)	
Mother's ethnic group	Muhajirs	78	31 (39.7%)	27 (34.6%)	20 (25.6%)	0.022
	Sindhi	52	33 (63.5%)	11 (21.2%)	8 (15.4%)	
	Memon	40	25 (62.5%)	6 (15.0%)	9 (22.5%)	
	Other	93	37 (39.8%)	34 (36.6%)	22 (23.7%)	
Pre-pregnancy Weight	Underweight	30	16 (53.3%)	10 (33.3%)	4 (13.3%)	0.457
	Normal	200	98 (49.0%)	57 (28.5%)	45 (22.5%)	
	Overweight	33	12 (36.4%)	11 (33.3%)	10 (30.3%)	
Number of children in home	0 (Primiparous)	107	51 (47.7%)	28 (26.2%)	28 (26.2%)	0.665
	1	91	46 (50.5%)	27 (29.7%)	18 (19.8%)	
	2	40	19 (47.5%)	15 (37.5%)	6 (15.0%)	
	3 or more	25	10 (40.0%)	8 (32.0%)	7 (28.0%)	
Male child at home	Primiparous	107	51 (47.7%)	28 (26.2%)	28 (26.2%)	0.701
	No	63	31 (49.2%)	21 (33.3%)	11 (17.5%)	
	Yes	93	44 (47.3%)	29 (31.2%)	20 (21.5%)	
Pregnancy planned	Yes	201	92 (45.8%)	59 (29.4%)	50 (24.9%)	0.209
	No	62	34 (54.8%)	19 (30.6%)	9 (14.5%)	
Infections during pregnancy	Yes	10	3 (30.0%)	2 (20.0%)	5 (50.0%)	0.116
	No	253	123 (48.6%)	76 (30.0%)	54 (21.3%)	
Work	Homemaker	210	104 (49.5%)	63 (30.0%)	43 (20.5%)	0.304
	Worked/Student	53	22 (41.5%)	15 (28.3%)	16 (30.2%)	
Choice of husband	Yes	90	33 (36.7%)	36 (40.0%)	21 (23.3%)	0.014
	No	173	93 (53.8%)	42 (24.3%)	38 (22.0%)	
Medication	Yes	145	84 (57.9%)	39 (26.9%)	22 (15.2%)	<0.001
	No	118	42 (35.6%)	39 (33.1%)	37 (31.4%)	

ACE-IQ = Adverse Childhood Experiences–International Questionnaire; Rs = Pakistani Rupees.

parallel pattern of results occurred for PS scores ($P = 0.045$ and $P = 0.002$, respectively). No significant group differences were found between women with one ACE and those with two or more ACEs, suggesting that the real impact of psychosocial distress was whether women had any ACEs or not.

3.3. PTB and socio-demographic/psychosocial factors

Neither the binary nor the frequency score of the ACE-IQ were significantly associated with PTB. Four variables were associated with PTB; mother's education ($P = 0.011$), mother's ethnic group ($P = 0.010$); age at birth of the first child ($P = 0.049$) and taking medication ($P = 0.006$) (Table 4a and 4b). Women with primary school education or less had a higher PTB rate (21.5%) than those with a

Table 2b
Comparison of ages for different levels of ACE-IQ binary.

		ACE-IQ Binary Categories			*P*-value
	Total n=263 mean (SD)	0	1	>=2	
		n = 126 mean (SD)	n = 78 mean (SD)	n = 59 mean (SD)	
Current age	26.8 (4.6)	26.7 (4.7)	27.3 (4.7)	26.3 (4.0)	0.454
Age at marriage	22.6 (3.4)	22.6 (3.4)	22.8 (3.4)	22.6 (3.4)	0.881
Age at birth of first child (or current age if primiparous)	23.7 (3.4)	23.8 (2.8)	23.9 (3.4)	23.8 (3.5)	0.913
		ACE-IQ Frequency Categories			*P*-value
	Total n=263 mean (SD)	0	1	>=2	
		178 mean (SD)	60 mean (SD)	25 mean (SD)	
Current age	26.8 (4.6)	26.7 (4.8)	27.5 (4.3)	25.7 (3.4)	0.257
Age at marriage	22.4 (3.3)	23.5 (3.5)	22.0 (3.5)	22.6 (3.4)	0.091
Age at birth of first child (or current age if primiparous)	23.6 (3.4)	24.6 (3.6)	23.1 (3.3)	23.8 (3.5)	0.103

ACE-IQ = Adverse Childhood Experiences–International Questionnaire; SD = Standard deviation

Table 3
Psychosocial scores at recruitment by level of ACE-IQ binary and frequency.

Psychosocial measure	Total n = 263 mean (SD)	Level of ACE-IQ binary 0	1	2+	*P*-value for difference in means within ACE-IQ binary category: Overall	0 & 1	0 & 2+	1 & 2+
		n = 126 mean (SD)	n = 78mean (SD)	n = 59mean (SD)				
Pregnancy-related anxiety (PRA)	11.9 (5.4)	11.5 (5.7)	12.1 (5.2)	12.7 (4.6)	0.326	0.442	0.141	0.481
Edinburgh (perinatal) depression scale (EPDS)	5.9 (5.4)	4.2 (4.3)	6.8 (5.5)	8.2 (6.3)	<0.001	<0.001	<0.001	0.128
Perceived stress (PS)	15.1 (5.6)	14.0 (5.3)	15.6 (5.6)	16.7 (5.8)	0.005	0.045	0.002	0.227
Psychosocial Measure	Total n=263 mean (SD)	Level of ACE-IQ Frequency 0	1	2+	*P*-value for Difference in Means within ACE-IQ frequency category Overall	0 & 1	0 & 2+	1 & 2+
		n = 178 mean (SD)	n = 60 mean (SD)	n = 25 mean (SD)				
Pregnancy-related anxiety (PRA)	11.9 (5.4)	11.8 (5.4)	12.0 (5.1)	12.9 (5.6)	0.647	0.855	0.343	0.467
Edinburg (perinatal) depression scale (EPDS)	5.9 (5.4)	5.1 (4.6)	7.2 (5.9)	8.4 (8.0)	0.002	0.009	0.004	0.343
Perceived Stress (PS)	15.1 (5.6)	14.7 (5.4)	15.2 (5.8)	17.6 (6.6)	0.047	0.533	0.014	0.067

ACE-IQ = Adverse Childhood Experiences–International Questionnaire; SD = Standard deviation

secondary, high school, college or university education (9.8%). Women from minority ethnic groups (i.e., other) had the highest PTB rate (18.3%) followed by women from the Memon group (15.0%). Women with PTB tended to have their first child at younger ages of about 1.3 years (15–16 months). These women also tended to have their first child at younger ages by about 1 year. It should, however be noted that 107 (40.7%) of the women were primiparous. Women who were on medications also had a higher PTB rate than those that were not (16% compared to 5%). There was no statistically significant relationship between psychosocial distress measures and PTB at any time point (Table 4c).

We investigated the possible interaction effect between medications and ACE on PTB. The association between taking medications during pregnancy and PTB was significant only among women with no ACEs (i.e., $P = 0.002$), but not for women with 1 or more ACEs. Similarly, since the ethnicity of mothers was associated with both ACE-IQ frequency and PTB, a similar investigation for possible interaction was conducted, but no interaction was found.

3.4. Parsimonious predictive model for PTB

Mother's education level, mother's ethnicity, taking medications during pregnancy, age at birth of first child or current age if primiparous and age at marriage were included in a multiple logistic regression model along with possible interaction effects between them, to determine a predictive model for PTB. Mother's ethnic group and taking medications during pregnancy were the only variables retained (Table 5). Although the likelihood of having PTB is higher for each of the ethnic groups compared to Sindhi, only the difference between Sindhi and "others" emerged as significant with "others" being 7.0 times more likely than Sindhi to have PTBs. Women who were taking medication were almost 4 times more likely to have PTBs compared to those who were not. Pairwise-comparison of different ethnic groupings revealed that the prevalence of PTB was marginally lower among Muhajirs and Memon compared to "other" ethnic groups. No significant interactions were found between any of the five factors included in the model.

4. Discussion

In our sample the rate of PTB was consistent with the 11% overall prevalence of PTB across 99 countries; however, rates as high as 15.7% have been reported for Pakistan (Blencowe et al., 2012; Lawn et al., 2010). No relationship was revealed between ACEs and PTB, which is in contrast with prior studies (Christiaens et al., 2015; Smith et al., 2016). Christiaens et al. (2015) and Smith et al. (2016) used different tools to measure ACEs in their studies. Furthermore, these studies (Christiaens et al., 2015; Smith et al., 2016) were conducted in two highly developed nations, Canada (Christiaens et al., 2015) and USA (Smith et al., 2016). Indeed, South Asian women may contextualize ACEs differently, particularly domestic violence, given societal acceptability and shared understanding (Bright et al., 2018). Three of the 13 indicators of ACE-IQ – bullying, witnessing community violence, and collective violence – are not part of the ACEs survey developed in the US (Felitti et al., 1998). Pregnant women report no collective violence, however, relatively many (17.2%) experienced community violence. An estimated 21.7% of pregnant women experienced the loss of one or both parents or guardians (death, divorce, separation). Few reported emotional neglect, and even fewer (<10%) reported emotional abuse, physical neglect or physical abuse. Environmental context may influence a pregnant women's appraisal of her life circumstances and stress reactivity through gene-environment interaction (i.e., epigenetics). Moreover, protective or strength-based (i.e., resilience) approaches adapted by those exposed to familial, social, and neighbourhood stress that is pervasive or persistent remains poorly understood (Leitch, 2017). In our sample, the number of ACEs and the ongoing

Table 4a
Categorical demographic and other variables: relationship to PTB.

Variable	Categories	n	No PTB n (%)	PTB n (%)	*P*-value
Location	Garden	100	86 (86.0%)	14 (14.0%)	0.124
	Hyderabad	68	59 (86.8%)	9 (13.2%)	
	Karimabad	61	59 (96.7%)	2 (3.3%)	
	Kharadar	34	30 (88.2%)	4 (11.8%)	
Father's education	No Formal School/Primary School	72	61 (84.7%)	11 (15.3%)	0.495
	High School Completed	60	55 (91.7%)	5 (8.7%)	
	Attended or Completed Post-Secondary Studies	74	68 (91.9%)	6 (8.1%)	
	Attended or Completed Graduate studies	57	50 (8.7%)	7 (12.3%)	
Mother's education	No Formal School/Primary School	65	51 (78.5%)	14 (21.5%)	0.011
	Secondary or High School Completed	59	54 (91.5%)	5 (8.5%)	
	Attended or Completed Post-Secondary Studies	92	83 (90.2%)	9 (9.8%)	
	Attended or Completed Graduate studies	47	46 (97.9%)	1 (2.1%)	
Household income	<Rs 10,000	37	29 (78.4%)	8 (21.6%)	0.207
	Rs 10,001–20,000	62	57 (91.9%)	5 (8.1%)	
	Rs 20,001–40,000	83	75 (90.4%)	8 (9.6%)	
	>Rs 40,000	70	64 (91.4%)	6 (8.6%)	
	Not Known*	11	9 (81.8%)	2 (18.2%)	
Mother's ethnic group	Muhajirs	78	74 (94.9%)	4 (5.1%)	0.010
	Sindhi	52	50 (96.2%)	2 (3.8%)	
	Memon	40	34 (85.0%)	6 (15.0%)	
	Other	93	96 (81.7%)	17 (18.3%)	
Pre-pregnancy weight	Underweight	30	27 (90.0%)	3 (10.0%)	0.706
	Normal	200	176 (88.0%)	24 (12.0%)	
	Overweight	33	31 (93.9%)	2 (6.1%)	
Number of children at home	0 (Primiparous)	107	96 (89.7%)	11 (10.3%)	0.111
	1	91	85 (93.4%)	6 (6.6%)	
	2	40	33 (82.5%)	7 (17.5%)	
	3 or more	25	20 (80.0%)	5 (20.0%)	
Male child at home	Primiparous	107	96 (89.7%)	11 (10.3%)	0.635
	Yes	63	54 (85.7%)	9 (14.3%)	
	No	93	84 (90.3%)	9 (9.7%)	
Pregnancy planned	Yes	201	176 (87.6%)	25 (12.4%)	0.248
	No	62	58 (93.5%)	4 (6.5%)	
Infections during pregnancy	Yes	10	9 (90.0%)	1 (10.0%)	1.000
	No	253	225 (88.9%)	28 (11.1%)	
Work	Homemaker	210	185 (88.1%)	25 (11.9%)	0.467
	Worked/Student	53	49 (92.5%)	4 (7.5%)	
Choice of husband	Yes	90	79 (87.8%)	11 (12.2%)	0.681
	No	173	155 (89.6%)	18 (10.4%)	
Medications	Yes	145	122 (84.1%)	23 (15.9%)	0.006
	No	118	112 (94.9%)	6 (5.1%)	

PTB = preterm birth; Rs = Pakistani Rupees

Table 4b
Mean (SD) of various ages by birth outcome.

	Birth Outcome No PTB n = 234 mean (SD)	PTB n = 29 mean (SD)	*P*-value*
Current age	26.8 (4.5)	27.0 (5.3)	0.839
Age at marriage	22.8 (3.4)	21.7 (3.4)	0.098
Age at birth of first child (or current age if Primiparous)	23.9 (3.5)	22.6 (3.2)	0.049

PTB = preterm birth; SD = standard deviation

Table 4c
Continuous demographic and other variables: relationship to PTB.

Psychosocial dimension	Total n = 263 mean (SD)	Birth outcome No PTB n = 234 mean (SD)	PTB n = 29 mean (SD)	*P*-value
Time 1				
PRA Score	11.9 (0.33)	12.1 (0.35)	10.7 (0.96)	0.195
EPDS Score	5.9 (0.33)	5.8 (0.34)	6.6 (1.26)	0.454
PS Score	15.1 (0.35)	15.3 (0.37)	13.6 (0.99)	0.121
	Total n = 234 mean (SD)	No PTB n = 0201 mean (SD)	PTB n = 24 mean (SD)	*P*-value
Time 2				
PRA Score	12.2 (0.28)	12.3 (0.29)	11.9 (0.96)	0.720
EPDS Score	6.8 (0.35)	6.8 (0.37)	7.3 (1.22)	0.696
PS Score	14.7 (0.39)	14.8 (0.42)	14.5 (1.11)	0.814

PTB = preterm birth; SE = standard error of the mean; PRA = pregnancy-related anxiety;
EPDS = Edinburgh Perinatal Depression Scale; PS = perceived stress

exposure of trauma was of little consequence as neither the WHO ACE-IQ binary nor frequency analytic methods showed any relationship with PTB. Our findings may be explained by the low report of ACEs among the pregnant women.

Although ACEs were not directly associated with PTB, knowledge about the presence of any ACEs was useful in determining whether taking medications would be predictive of PTB or not. The relationship between PTB and taking medications was significant only among women without ACEs (i.e., binary method of analysis). Specifically, all women without risk factors (i.e., no ACE and no medication) had normal deliveries, whereas PTB occurred among women with either ACE or medication use. The safety and efficacy of multiple micronutrient supplementation for pregnant women in low resource countries, particularly among women with no formal education or in whom micronutrient supplementation begins early in pregnancy, has been questioned given its association with perinatal mortality (Kawai et al., 2011). In view of the inherent risk for some, the WHO does not recommend universal multiple micronutrient supplementation for pregnant women. A systematic review and meta-analysis of ten randomized controlled trials (n = 1586 women with unexplained

Table 5
Odds ratios and confidence intervals in parsimonious predictive model for preterm birth.

Exposure	No PTB n = 234	PTB n = 29	Odds Ratio	95% CI Lower	Upper	*P*-value
Mother's ethnic group	n (%)	n (%)				
Muhajirs	74 (94.9%)	4 (5.1%)	2.24	0.38	13.19	0.372
Sindhi	50 (96.2%)	2 (3.8%)	1.0	referent		
Memon	34 (85.0%)	6 (15.0%)	5.06	0.95	26.93	0.057
Other	96 (81.7%)	17 (18.3%)	7.0	1.53	32.08	**0.012**
Medication during pregnancy	n (%)	n (%)				
Yes	122 (84.1%)	23 (15.9%)		referent		
No	112 (94.9%)	6 (5.1%)	3.56	1.35	9.35	0.01

PTB-preterm birth; CI = confidence interval

recurrent miscarriage) found treatment with progestogens (i.e., progestin medication like Duphaston) in early pregnancy (i.e., first trimester and <16 weeks' gestational age) reduced risk of recurrent miscarriage without adverse effects of PTB although the quality of the included studies was queried (Saccone et al., 2017). The apparent negative association between taking medications and PTB can be explained by the fact that all the women with no identified risk factors (no ACE and no medication/supplement) had normal delivery, while some of the women with some risk factors (ACE-IQ > 0 or evidence of taking medication) had PTB as would be expected.

We found an association between location and ACEs with women from Kharadar being most likely to experience an ACE score > 2. Kharadar, the core and textile industry of Karachi, differs from the other centres with respect to its inadequate infrastructure, levels of poverty, maternal literacy, and socio-cultural background. Residents in Kharadar, an old innercity neighbourhood, confront both perceptions of and actual state and non-state violence including social, state and political violence (Viqar, 2018). It is not unusual for movements to be restricted in the entire old city area when turf wars are active. Area or neighbourhood level deprivation which is a geographically based composite measure of the socioeconomic characteristics (e.g., income, employment, education, and proximity of services) is associated with poor health (e.g., blood pressure and diabetes), poor mental well-being (e.g., depression, and anxiety), fewer years of formal education, and risk behaviours (e.g., smoking, alcohol and drug use) (McCann et al., 2018; Adhikari Dahal et al., 2017). Women's social, economic, and political context may explain the differential exposure to ACEs across women in the four sites (Metzler et al., 2017).

A higher PTB rate was also associated with mother's ethnic group. Women from the Sindhi ethnic group, the oldest and main ethnic group in Pakistan, were least likely to have PTB. Both the number of ACEs and intensity of the ACEs was associated with mother's ethnic group. The majority of Sindhi women had no ACEs and were less likely to have 2 or more ACEs than other women. When examining the frequency of ACEs, however, minority ethnic groups and Sindhi women (13% and 11.5%, respectively) reported two or more instances of ACE frequency. ACEs limit life opportunities such as education (Metzler et al., 2017). For women enrolled in our study higher maternal education was protective against PTB. Education, a proxy of socioeconomic status, may combine with other individual level indicators including medication use, mental health (i.e., depression, pregnancy-related anxiety, stress) and neighborhood circumstances to influence risk of PTB in women (Adhikari et al., 2019; Shaikh et al., 2011). Both ACE binary and frequency were related to EPDS and PS. The means of the psychosocial scores increased with the number of ACE-IQ. However, the significance of the relationship between ACE and both PRA and EPDS was due to a significant difference between the means of PRA and EPDS among women with no ACE and women with one or more ACEs.

5. Limitations

Our findings are somewhat limited by the relatively small sample size which does not allow generalisation to the entire country. Our conclusions are therefore, specific to Karachi, Pakistan, and should be replicated in other LMI countries. In conclusion, our data provides preliminary evidence that pathways to PTB for women in LMI countries may differ from those commonly reported in high-income countries and need to be modelled differently with ACEs interacting in complex ways with women's unique emotional reactivity, behavioural response patterns to emotional distress (e.g., medication use), and socio-cultural context (Premji et al., 2015).

Funding source

This work was supported by the Canadian Institutes of Health Research Planning Grant [grant number 264531] and Aga Khan University, University Research Council Multi-disciplinary Project Grant [grant number 144005SOANM].

CRediT authorship contribution statement

Kiran Shaikh: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Shahirose Sadrudin Premji:** Conceptualization, Writing - original draft, Writing - review & editing. **Sharifa Lalani:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Ntonghanwah Forcheh:** Writing - review & editing. **Aliyah Dosani:** Conceptualization, Writing - review & editing. **Ilona S Yim:** Writing - review & editing. **Pauline Samia:** Conceptualization, Writing - review & editing. **Christopher Naugler:** Conceptualization, Writing - review & editing. **Nicole Letourneau:** Writing - review & editing.

Declaration of Competing Interest

None.

Acknowledgements

Maternal Infant Global Health Team (MiGHT) Collaborators in Research members (alphabetical): Naureen Akber Ali, Amber Amirali, Kishwer Arif, Neelofur Babar, Christine Dunkel Schetter, Fazila Faisal, Farooq Ghani, Nasreen Ishtiaq, Nigar Jabeen, Arshia Javed, Imtiaz Jehan, Fouzia Karim, Rabia Khuwaja, Mohamoud Merali, Ayesha Mian, Qamarunissa Muhabat, Joseph Wangira Musana, Sidrah Nausheen, Christine Okoko, Almina Pardhan, Erum Saleem, Rozina Shehzad, Sana Siddiqui, and Salima Sulaiman. We wish to express our sincere appreciation to the entire team!

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.01.180.

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