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Adverse childhood experiences and implications of perceived stress, anxiety and cortisol among women in Pakistan: a cross-sectional study

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ABSTRACT

Objectives Adverse childhood experiences (ACEs) are linked to poor maternal mental health. The goal of this study is to examine the associations between ACEs and multiple manifestations of stress (including perceived stress, anxiety and cortisol) among mothers in rural Pakistan.

Design This study used a cross-sectional design. Mothers were originally recruited during their third trimester of pregnancy and followed until 36 months post partum. Cortisol was collected at 12 months post partum, and self-report data were collected at 36 months post partum.

Setting All participants reside in rural villages in Rawalpindi, Pakistan. The measures were administered at home visits by field interviewers.

Participants Data were collected from 889 mothers. All mothers in the sample provided data on ACEs and perceived stress, 623 provided data on anxiety and 90 provided hair cortisol.

Primary and secondary outcomes measures ACEs were captured retrospectively using an adapted version of the ACE International Questionnaire, and represented as a continuous variable and subdomains (neglect, home violence, family psychological distress, community violence). Primary outcomes included perceived stress measured with the Cohen Perceived Stress Scale (PSS) and anxiety measured with the Generalised Anxiety Disorder-7 scale (GAD-7). Hair-derived cortisol was included as a secondary outcome. Generalised linear models with cluster-robust SEs were used to estimate associations between ACEs and the outcome variables.

Results All models featured positive associations between ACE items and PSS. The continuous total ACE score (B=0.4; 95% CI 0.0 to 0.8) was associated with higher anxiety symptoms on the GAD-7. Home violence (B=6.7; 95% CI 2.7 to 10.8) and community violence (B=7.5; 95% CI 1.4 to 13.6) were associated with increased hair cortisol production.

Conclusions All four ACE domains were associated with elevated levels of perceived stress, anxiety and cortisol, with varying precision and strength of estimates, indicating that the type of ACE has a differential impact. This study informed our understanding of the differential impact of specific ACEs on perceived stress, anxiety and hypothalamic pituitary adrenal-axis functioning, providing

Strengths and limitations of this study

► We investigated the impact of adverse childhood experiences (ACEs) in a low-income and middle-income country context, where ACEs have been understudied yet pose a significant public health burden.

► We modelled subdomains of ACEs to investigate the differential effects of varying types of adversity exposure, in addition to modeling the continuous ACEs score.

► We also studied multiple related outcomes—perceived stress, anxiety and hair cortisol—to discern nuances among them.

► The ACEs questionnaire involved recall bias due to questions asking about events that occurred years, if not decades ago, though the ACEs questionnaire was designed to be asked retrospectively.

► The study design was cross-sectional, limiting the potential to assess a temporal link between ACE exposure and the outcome variables.

implications for future clinical intervention and research development.

OBJECTIVES

The prevalence of adverse childhood experiences (ACEs) is extremely high, with population estimates ranging from 50% to 70% in low/middle-income countries (LMICs).[1] A robust literature links ACEs with compromised physical health, mental health and overall functioning in adulthood.[2–6] Those exposed to ACEs are less likely to obtain high levels of education, leading to financial insecurity, lower socioeconomic status and a lack of psychosocial resources.[5] The compounding nature of adversity is especially impactful in LMICs where rates of ACEs are high and other stressors, such as poverty, may lead to and co-occur with ACEs.[7 8] One developing setting in which ACEs have been

understudied is Pakistan. Of the few studies set in Pakistan, most broaden the definition of ACEs to include broadly negative life events like food insecurity and poor family support,[9 10] making it difficult to compare findings across ACEs studies in other contexts. In addition, while the majority of past studies on these topics sample well-educated, urban populations, the majority of Pakistani women have spent their life in rural areas, which are tied to unique stressors, such as low education and literacy of women and transportation barriers.[11–14] Assessing the effects of ACEs in this context is critical for understanding the global impact of ACEs exposure.

The impact of ACEs on maternal mental health is of particular concern; maternal mental health may function as a mediator between maternal ACE exposure and child mental health. Mothers who experience ACEs may be more likely to suffer from mental health difficulties that interfere with their ability to provide safe, nurturing and sensitive environments for their children.[15] Children in such environments may then be more likely to develop mental health problems, perpetuating a cycle of intergenerational trauma.[16] Studies of ACEs and maternal mental health may inform early intervention supporting the mother in promoting her own emotion regulation as well as the well-being of her child.[17] Informed by life course theory's linkage of adult disease risk to psychosocial exposures stemming from childhood, understanding the associations between ACEs and adult health may offer important insights into preventing compounding health issues throughout life for both mothers and children.[18]

While the overall literature linking ACEs to mental health is robust, several key questions are not well understood. The first is to what extent examining the unique effects of different types of ACEs is important for elucidating how early experiences impact adult functioning. Much of past work has focused on specific ACEs (eg, sexual abuse) or the cumulative effect of ACEs; often, domain-specific (eg, abuse, neglect, household dysfunction) results have either not been reported or have been ambiguous.[19–21] Nonetheless, multiple researchers have pointed to the utility of separating ACEs into distinct domains. There is a lack of consensus about which types of ACEs are related to women's mental health.[22] For instance, Negriff[23] found that in the USA, experiencing neglect, but not physical abuse, predicted anxiety symptoms in adolescence and ACEs related to child maltreatment were more predictive of mental health outcomes than ACEs related to household dysfunction.[23] In our team's prior work with a cohort of women in Pakistan at 36 months post partum, we have found that exposure to community violence was much more strongly correlated with maternal depression than other domains such as neglect.[24] A significant potential driver of different findings is the diversity of social, economic and cultural contexts in which the ACEs take place. Hence, studies from multiple geographic regions and population groups make important contributions towards better understanding of how various ACEs may differentially impact mental health.

A second area of inquiry focuses on the biological stress-related pathways linking ACEs to various health outcomes. Specifically, there is evidence that ACEs impact stress regulation systems, including the hypothalamic pituitary adrenal (HPA) axis and its end product of cortisol.[25–27] ACEs are associated with both hyperactivation and hypoactivation of the HPA axis, leading to elevated or reduced cortisol levels, respectively.[28–30] Some studies indicate that exposure to acute stress leads to initial hyperactivation of the HPA axis, while chronic, prolonged stress leads to reduced activity of the HPA axis.[31 32] Salivary cortisol involves methodological disadvantages, stemming from high sensitivity to short-term confounds, such as circadian rhythm, compared with hair-derived cortisol.[33–35] Therefore, HPA axis hormones extracted from hair samples capture chronic stress and HPA axis activity over the course of months, which may be an important mediator between early life experiences and later mental health.[36 37] The majority of this research has also been conducted in high-income settings, further demonstrating the need for studies to be conducted in low-resource settings including Pakistan.

In the current study, we examine how retrospectively reported ACEs are associated with multiple stress-related outcomes later in life including anxiety, perceived stress and hair-derived cortisol in a sample of mothers living in rural Pakistan. We hypothesise that ACEs in all domains will predict heightened levels of perceived stress, anxiety symptoms and hair cortisol. Studies have linked ACEs with experiences of perceived stress,[38–40] increased risk for anxiety disorders[41–43] and altered cortisol[29 30 44] in adulthood, although none of this work has been conducted in Pakistan. Perceived stress and anxiety capture related but distinct constructs associated with psychological stress, with perceived stress representing short-term feelings of being overburdened and anxiety representing chronic worry and physiological dysregulation consistent with generalised anxiety disorder (GAD). Cortisol represents a physiological correlate of stress. Understanding how ACEs may differentially relate to these outcomes can shed light on the nuanced associations between childhood experiences and women's well-being.

METHODS
Study design and participants
The data in the present analysis come from mothers of the Bachpan cohort, a longitudinal birth cohort of mother–child dyads in rural villages in Rawalpindi, Pakistan, which is north of the Punjab Province (Sikander *et al*, 2015).[45] In this study, we conducted a secondary analysis using data collected at the 36-month assessment. One of the purposes of the Bachpan cohort was to evaluate the impact of a peer-delivered, community-based perinatal depression intervention, embedded within the cohort, on maternal mental health and child development.[46] Pregnant women from 40 village clusters were screened for depression and invited to participate

in the study. Twenty of the 40 village clusters were randomised to receive both the perinatal intervention and enhanced usual care, while the other 20 clusters received enhanced usual care alone. The intervention consisted of both individual and group-based sessions focused on behavioural activation, problem-solving and peer support. Participants engaged in weekly sessions during the prenatal period, biweekly sessions between birth and 6 months and monthly sessions between 7 and 36 months. Past research has shown that those receiving the intervention showed reduced depressive symptoms at 6 months; however, the effects of the intervention weakened over time.[47 48] In addition, an equal number of non-depressed pregnant women were recruited and followed in parallel as part of the Bachpan cohort to understand the degree to which the intervention could mitigate the risk of intergeneration transmission of poor mental health from mothers to their children.[47] Women were assessed at baseline (during their third trimester of pregnancy) and at an additional five timepoints: 3, 6, 12, 24 and 36 months post partum. At the 36-month assessment, participants completed questionnaires assessing ACEs, anxiety and perceived stress. In addition, a subsample of participants at the 12-month interview, were asked to provide hair for cortisol assay. Of the 1154 women included at baseline, 889 participated in the 36-month questionnaire, providing information on ACEs and perceived stress. Due to a delay in administering the anxiety assessment, 623 participants provided information on anxiety symptoms. We approached a randomly selected subsample of 107 women for hair cortisol collection, and of those, 93 provided valid samples. Finally, 90 mothers provided both hair cortisol and ACEs measurement. The outcomes were collected at home visits by field interviewers.

Measures
Adverse childhood experiences
ACEs were assessed retrospectively at the 36-month data collection period using an adapted 12-item ACE International Questionnaire (WHO, 2018). It has been validated in other LMIC settings, namely Malawi and Nigeria.[49 50] The ACE International Questionnaire was adapted to the Pakistani context based on feedback from the local field team to remove the sexual abuse questions. This was mainly due to concerns around stigma. Data collection was conducted in participants' homes, where the team was not able to guarantee privacy and where respondents might feel uncomfortable disclosing information around childhood sexual abuse. The questionnaire was also translated into Urdu. To discern the impacts of different ACE subtypes and methods of representation, we created a summed score and indicators for the theorised domains: neglect, family psychological distress, home violence and community violence (table 1). The domains are dichotomous, representing exposure to any of the ACEs comprising the domain.

Perceived stress
Perceived stress was measured using the Perceived Stress Scale (PSS). The PSS is a 10 item instrument that measures the degree to which life situations are appraised as stressful in the last month.[51] The summed score ranges from 0 to 40 and has demonstrated reliability and validity in South Asia.[52 53] In the current sample, the PSS demonstrated high reliability ($\alpha=0.91$).

Anxiety
Anxiety was measured using the seven-item version of the Generalised Anxiety Disorder-7 screening tool (GAD-7). The frequency of symptoms in the last 2 weeks is assessed on a 4-point Likert scale. The summed score ranges from 0 to 21, with a cut-off of 10 typically representing a clinically significant level to identify probable cases of genaeraliesd anxiety disorder.[54] The total summed GAD score was used in analyses. The GAD-7 measure has demonstrated reliability and validity in Pakistan.[55] In the current sample, this scale demonstrated high reliability ($\alpha=0.93$). In the overarching study, the intervention did not show sustained effects on anxiety symptoms.[47]

Cortisol
Hair samples were collected using a standard protocol: approximately 200 strands of hair were cut from the posterior vertex. Research suggests that 1 cm of hair reflects hormonal output for the previous month.[56] The present analysis uses 2 cm of hair, reflecting HPA-axis hormone output for the past 2 months. No participant reported hair treatment, hair product, oral or topical steroid usage. Cortisol was extracted and measured by Dresden LabService using standard liquid chromatography-mass spectrometry.[57] We did not observe any outliers. Levels are reported as pg/mg.

Covariates
Informed by existing literature, several variables were selected for the models to adjust for design characteristics and to identify potential confounders. These included maternal age, natal family's history of mental illness, participant level of educational attainment, baseline depression, peer-delivered perinatal intervention allocation status and assessor at 36 months.[58]

Statistical analysis
For this cross-sectional analysis, a series of generalised linear models with an identity link were created to estimate coefficients for the total PSS and GAD scores as well for the maternal hair cortisol concentrations. All models used cluster-robust SEs to account for clustering at the village cluster level. The PSS and GAD models were adjusted for baseline depression and treatment allocation status, mother's age at baseline and education level, history of natal family mental health and assessor at 36 months. For each outcome (perceived stress, GAD and hair cortisol), we examined associations with: (1) the number of endorsed ACEs modelled as a continuous indicator and (2) dichotomous indicators for each domain

Table 1 Adverse childhood experience international domain and question definitions

Description	Question
Neglect	
Emotional neglect	Caregiver did not understand your problems/worries; did not know what you were doing with your free time
Physical neglect	Caregiver did not give you enough food or sending you to school even it could easily been done; too drunk/intoxicated by drugs to take care of you
Family psychological distress	
Alcohol and/or drug misuser in household	Lived with a household member who was a problem drinker, alcoholic or misused street/prescription drugs
Incarcerated household member	Lived with a household member who ever sent to jail or prison
Someone chronically depressed, mentally ill, institutionalised or suicidal	Lived with a household member who was depressed, mentally ill or suicidal
One or no parents, parental separation or divorce	Parents ever separated/divorced, or father/mother/guardian died
Home violence	
Physical abuse	You being spanked/slapped/kicked/punched/beaten up; or being hit/cut with an object by parents/guardian
Emotional abuse	You were yelled at/screamed at/sworn at/insulted or humiliated, or were threatened/abandoned, thrown out by parents/guardian
Household member treated violently	Saw or heard a parent/household member being yelled at/screamed at/sworn at/insulted or humiliated; being slapped/kicked/punched/beaten up; or being hit/cut with an object
Community violence	
Bullying	Being bullied
Community violence	See or hear someone being beaten up, stabbed, shot or being threatened with a knife or gun in real life
Collective violence	Forced to go and live in other place; experienced disruption of home due to these events; you or family member or friend killed or beaten up by soldiers, police, gangs or militia

of ACEs (neglect, family psychological distress, home violence and community violence). Since the cortisol subsample was included as an exploratory analysis, which we will build on in future work, the analyses were not statistically powered. Additionally, due to the mental health focus of the intervention, we examined differences in each outcome by intervention group. We also examined whether the association between ACEs and each outcome was moderated by intervention group (online supplemental table 1). Stata V.16.1 was used for data analysis (StataCorp). All presented betas are unstandardised.

Patient and public involvement

Patient collaborators were not directly involved in the design, recruitment or dissemination of this study. However, women in the recruitment populations have expressed a high degree of interest in the issue of maternal mental health.

RESULTS
Descriptive statistics

Our analytic sample consisted of 889 women who were interviewed at 36 months post partum. Baseline (third

trimester of pregnancy) participant characteristics of these participants are displayed in table 2. The majority (66.4%) received at least a fifth-grade education and had one to three children (62.5%); the mean age (SD) at baseline was 26.7 (4.4) years old. About 10% reported growing up in a household with a family number who had a mental health illness. The mean (SD) total score on the PSS-10 stress scale was 12.0 (8.8).

Fifty-eight per cent of women experienced at least one ACE (table 3), with a mean (SD; minimum, maximum) total number of ACEs of 1.2 (1.4; 0, 10). Among the 12 specific ACE items, emotional abuse (33.1%), physical abuse (23.5%) and emotional neglect (15.1%) were the most common. The most prevalent ACE domain was home violence (38.3%), followed by neglect (19.9%), family psychological distress (15.8%) and community violence (6.6%) (table 3). The distribution of ACEs was similar across the GAD and cortisol subsamples.

Of the 623 women present at the 36-month wave that completed the GAD-7, the mean (SD) total score was 4.0 (5.4) and 101 of the 623 participants (16.2%) had a score above the clinically significant cut-off of 10, which

Table 2 Demographic features of mothers in the Bachpan cohort study

Descriptor	ACEs and PSS, n=889	
	N/Mean	%/SD
Baseline (third trimester of pregnancy) characteristics		
Age	26.7	4.4
Education>5 th grade	590	66.4%
Living with mental health issue in the natal home	96	10.80%
Living children		
First pregnancy	258	29.0%
1–3 children	556	62.5%
4+ children	75	8.4%
Number of rooms, mean	4.2	1.9
People per room, mean	2.4	1.7
Socioeconomic status quintiles, mean	2	0.05
Nuclear family	113	12.7%
Baseline PHQ-9 total	8.4	6.7
Outcome variables from 36-month postnatal interview		
Total Perceived Stress Score (PSS), mean	12	8.8
Total Generalised Anxiety Disorder Score (GAD), mean, N=623	4	5.4
Hair-derived cortisol, mean, N=90 (pg/mg)	12.06	9.72

ACE, adverse childhood experience; PSS, Perceived Stress Scale.

Table 3 Maternal ACE characteristics in full sample

Description	Sample, N=889	
	N/Mean	%/SD
Neglect		
Emotional neglect	134	15.1%
Physical neglect	49	5.5%
Family psychological distress		
Household alcohol and/or drug use	24	2.7%
Incarcerated household member	16	1.8%
Depressed, mentally ill, institutionalised or suicidal household member	21	2.4%
One or no parents, parental separation or divorce	97	10.9%
Home violence		
Physical abuse	209	23.5%
Emotional abuse	294	33.1%
Household member treated violently	130	14.6%
Community violence		
Bullying	12	1.4%
Community violence	60	6.8%
Collective violence	4	0.5%
Domains		
Neglect	173	19.9%
Family psychological distress	143	15.8%
Home violence	349	38.3%
Community violence	64	6.6%
Number of ACEs		
0 ACEs	369	41.5%
1 ACE	239	26.8%
2 ACEs	139	15.6%
3 ACEs	82	9.2%
4+ACEs	61	6.8%
Any ACE Exposure	520	58.5%
Total number of ACEs	1.2	1.4

ACE, adverse childhood experience.

indicates moderate anxiety and signifies clinically significant GAD cases (online supplemental table 2).

There were no significant differences regarding descriptive characteristics between the three samples (N=889 for perceived stress, N=623 for anxiety, N=90 for cortisol). Compared with the PSS group, women in the GAD sample tended to be younger (M=26.7 in the PSS group, M=20.6 in the GAD group) (online supplemental table 2). The mean number of ACEs was higher in the cortisol subsample; fewer experienced 0 ACEs (24.4% in the cortisol group, 41.5% in the PSS group) and more experienced 4 or more (12.2% in the cortisol group, 6.8% in the PSS group). The cortisol subsample also experienced home violence at a higher rate compared with the PSS sample (52.2% vs 38.3%).

We also tested differences in the outcome variables by intervention group. Among women who were depressed at baseline, there were no significant differences in the PSS (p=0.38), GAD (p=0.23) or hair cortisol (p=0.33) based on whether they were assigned to the intervention or control group.

Perceived stress
The continuous total ACE indicator was associated with a higher PSS score (table 4, panel 1, model 1, B=1.0,

95% CI 0.7 to 1.3) at 36 months post partum, meaning that for every 1-point increase on the ACE scale (in other words, exposure to an additional adverse event), indicated a 1-point increase on the PSS. Higher scores on each of the ACE domains, family psychological distress, home violence and community violence, were associated with higher perceived stress.

Anxiety
The continuous total ACE score was associated with higher anxiety symptoms on the GAD-7 at 36 months post partum (table 4, panel 2, model 1, B=0.4; 95% CI 0.04

Table 4 Maternal ACEs and perceived stress, anxiety symptoms and hair cortisol levels at 36 months post partum

| Model | Predictor | Panel 1 | | Panel 2 | | Panel 3 | |
| | | Stress (PSS), N=889 | | Anxiety (GAD-7), N=623 | | Hair-derived cortisol, N=90 | |
		B	95% CI	B	95% CI	B	95% CI
1	ACE total	1.0*	0.7 to 1.3	0.4*	0.04 to 0.8	1.8*	0.6 to 3.0
2	Neglect	1.0	−0.5 to 2.6	−0.8	−2.3 to 0.8	2.4	−2.9 to 7.7
3	Family psychological distress	3.0*	1.3 to 4.7	1.6*	0.3 to 2.9	0.2	−6.2 to 6.6
4	Home violence	1.6*	0.6 to 2.7	0.7	−0.2 to 1.5	6.7*	2.7 to 10.8
5	Community violence	3.0*	1.1 to 4.9	1.6	−0.6 to 3.8	7.5*	1.4 to 13.6

Models take into account clustering at the village cluster level using cluster robust SEs, and models are adjusted for mother age at baseline, education level, natal family history of mental health, baseline depression and treatment status, and assessor.
*p<0.05.
†B values are in comparison to 0 ACE level.
ACE, adverse childhood experience; GAD-7, Generalised Anxiety Disorder-7; PSS, Perceived Stress Scale.

to 0.8). Anxiety symptoms were most strongly associated with a history of family psychological distress (model 4, B=1.6; 95% CI 0.3 to 2.9).

Cortisol
In the cortisol subsample, experiencing higher levels of ACEs was correlated with higher cortisol levels (table 4, panel 3). Of the specific ACEs domains, home violence (model 5, B=6.7; 95% CI 2.7 to 10.8) and community violence (model 6, B=7.5; 95% CI 1.4 to 13.6) were associated with increased hair cortisol.

DISCUSSION
The purpose of this study was to examine the impact of retrospectively reported ACEs on self-reported perceived stress, anxiety symptoms and hair cortisol in a sample of mothers residing in rural Pakistan. Our results revealed that ACEs are associated with increased perceived stress and anxiety later in adult life. These findings contribute to previous work indicating that the number of ACEs an individual experiences predicts their psychological functioning in adulthood.[20 21 59] We found that an increased total ACE score predicted increased stress, anxiety and cortisol. The individual domains of ACEs did not reliably predict adult stress across outcome types. Together, these results suggest that the cumulative effect of multidimensional early adversity, as captured by a continuous ACE measure, may be more important in predicting adult stress than the individual domains of adversity.

A higher percentage of our sample experienced at least one ACE compared with other study samples set in Pakistan, likely due to the study sample being collected from a rural population with unique sources of stress and adversity.[9 60] Indeed, additional studies set in rural contexts were needed. This prevalence was comparable to samples in other LMICs.[61 62] In our sample, the continuous ACEs score, as well as most ACEs domains (including family psychological distress, home violence and community violence) were associated with perceived stress. The accumulation of disadvantages (ie, a higher number of

ACEs) increases the likelihood that individuals who were exposed to ACEs experience a stressful environment later in life, potentially explaining the predictive power of many domains of ACEs on perceived stress.[63]

The continuous ACE score and the family psychological distress domain were associated with anxiety. These findings suggest that many domains of ACEs are associated with current perceptions of life stress, but only family psychological distress was linked to anxiety. The family psychological distress domain encompasses several ACEs (eg, parental separation, parental substance use) related to uncertainty and loss, which may be particularly impactful for the development of anxiety symptoms compared with the experience of stress. Indeed, experiences of loss and intolerance of uncertainty are indicated in the development of anxiety disorders.[64 65] In addition, these findings may reflect the heritability of anxiety disorders. Mothers whose parents suffered from anxiety may be more likely to have experienced family psychological distress as children, and may also be more likely to experience anxiety as adults.[64 65]

When examining the association between ACEs and hair cortisol, we found that the continuous ACE score or experiencing home violence were significant predictors of increased hair cortisol. This partially aligned with our hypothesis that early adversity is associated with increased HPA axis activity, and a subsequent increase in cortisol production.[25 66] These results add to the body of evidence linking ACEs to HPA axis hyperactivity. Supporting our results, a study in India analysed hair cortisol in children and found it linked with adversity.[67] Other studies have shown that among early life experiences, violence particularly has a potent impact on re-programming the HPA axis.[68] Past research examining stress exposure and cortisol has been mixed, with studies indicating that both high and low levels of cortisol are associated with chronic stress exposure.[69] Chronic stress may lead to an initial increase of HPA axis activity followed by a decrease in activity due to the HPA axis' negative feedback loop. Our results would suggest that early exposure to violence

is associated with increased activation of the HPA axis in adulthood. However, it is important to consider chronic suppression of the HPA axis as a potential outcome of early life stress. Furthermore, we did not control for additional factors that may contribute to hair cortisol concentration, including maternal BMI, hair-washing, recent stress exposure and illness. Future studies would benefit from a larger sample size to more fully investigate the relationship between ACE exposure and cortisol.

In LMICs, home violence in the form of interpersonal violence is particularly common, which is also reflected in our sample.[70 71] Home violence was the only domain that significantly predicted cortisol, possibly because it is linked to consequences that are emotional in nature: isolation, fear, guilt, low self-esteem.[72] Violence experienced at home may be internalised to a greater extent because it is physical, occurring closer to the child with a large presence in the child's life. Domestic violence also increases the risk for other kinds of abuse.[73] Young girls living in households with domestic violence are at risk for developing internalising mental health issues.[74] Importantly, we did not control for current interpersonal violence, which might interact with earlier adverse exposures and mediate HPA axis activity. We also did not find associations between the emotional abuse items and cortisol. Threatening, violent behaviours lead to the activated kinds of outcomes we focused on compared with ones that stem from neglectful experiences, which tend to be emotional in nature.[75]

Past research has suggested that experiences of deprivation (such as neglect) have distinct effects on development from experiences of threat (such as abuse or violence exposure). Specifically, researchers have found that deprivation experiences are associated with deficits in cognitive control and language development, whereas experiences of threat are more strongly associated with decreased emotion regulation and hypersensitivity to threat.[76–79] The outcomes measured in this study (stress, anxiety and cortisol) may be more strongly associated with threat experiences rather than deprivation. Future studies interested in capturing the full scope of the effects of ACEs may benefit from also including outcomes related to individuals' cognitive functioning.

This study benefited from a number of strengths. In particular, we investigated the impact of ACEs both continuously and as domains (neglect, home violence, family psychological distress, community violence). In particular, few prior studies have examined childhood adversity in the form of neglect.[80] Neglect is the most common type of maltreatment, increasing the importance to explore it in research.[80 81] Thus, we broke neglect into its subtypes of emotional and physical. The findings concerning neglect differed from the other domains, and future studies should examine neglect separately in addition to investigating its impact alongside other types of ACEs. In addition to modelling ACEs in multiple ways, we also approached the outcomes from two angles—perceived stress and anxiety—to discern nuances

between the two seemingly similar yet ultimately distinct constructs. The results of our study point to their distinctive relationships with ACEs. Additionally, the inclusion of the cortisol subanalysis is another way to approach the study of stress and anxiety, with cortisol representing a biological contrast to behavioural self-report measures, PSS and GAD-7. Finally, our study was situated in an LMIC context, where ACEs have been understudied yet pose a significant public health burden.[82]

These results should be interpreted in the context of several limitations. First, the study design was cross-sectional, limiting the potential to assess a temporal link between ACE exposure and the outcome variables. The cortisol subanalysis included a relatively small sample (n=90). Although this subanalysis was not able to be statistically powered, we intend to build on our findings to inform future work with this measure. Additionally, cortisol may not be as comparable to GAD-7 and PSS as it was measured at a different timepoint (12 months post partum vs 36 months post partum). We did not control for current depression in this sample as it is highly correlated with stress, anxiety and hair cortisol.[35 37] In this study, we did not intend to test the effect of ACEs on stress, anxiety and cortisol distinct from other, often comorbid, mental health concerns, such as depression. However, depression may be important to consider in future studies as it may serve as a confounder influencing both retrospective self-report of childhood experiences and reports of stress. In addition, depression may be a mediator linking ACEs to later stress, anxiety and cortisol.

Another limitation is that the ACEs questionnaire involved recall bias due to questions asking about events that occurred years, if not decades ago, although the measure we used was designed to be asked retrospectively.[83] All measures were self-reported and focused on the appraisal of experiences rather than the actual objective content, providing another pathway to produce subjective results.[37 84] Retrospective reporting may be limited because it relies on participants' memories of their childhood experiences; however, these reports may be relevant for understanding adult mental health. Newbury *et al* found that although both retrospective and prospective reports of maltreatment (which encompassed physical/emotional/sexual abuse and/or emotional/physical neglect) were associated with psychopathology, the strongest associations were discerned with the retrospective reports,[83] a finding reinforced by other studies.[85–87] Furthermore, there was low concordance between prospectively and retrospectively reported cases of maltreatment. Understanding the mechanisms behind these differential results should be further investigated in future work as this study and others suggest that whether and how an individual remembers ACEs, rather than what ACEs were experienced, *may be relevant for adult outcomes.*

A related limitation to the collection of data was that we did not measure childhood socioeconomic status and instead used participant education level as a proxy. We also did not include current stressful life events and

violence exposure. The relatively wide confidence intervals indicate that our results warrant further follow-up with larger samples.

One important consideration is the potential impact of the intervention on the study outcomes. The broader intervention that this study is embedded in could have had priming effects on the participants. However, we did not see effects of the intervention on perceived stress or anxiety in this sample, indicating that the relationship between ACE exposure and mental health was independent of the intervention (online supplemental table 1).

Due to the potential risk to respondents and under-reporting, we excluded the ACE questions related to sexual abuse, presenting an additional limitation. A meta-analysis reported increasing burden of childhood sexual abuse on adult-onset mental and physical health in LMICs, as well as the need to understand how to support individuals who have faced such trauma.[88] Childhood sexual abuse survivors face a lifetime of psychological distress, with differing effects on mental health compared with other types of ACEs.[89] By excluding childhood sexual abuse from our study, we may not have captured the full extent of participants' exposure to early adversity, nor we were able to capture the unique association between childhood sexual abuse and adult outcomes in this sample.

These results inform our understanding of how ACEs are associated with perceived stress, anxiety and HPA-axis functioning. ACEs were associated with heightened levels across all three domains of perceived stress, anxiety and cortisol, with varying precision and strength of estimates. Our study attempts to disentangle adversity into subtypes (neglect, home violence, family psychological distress, community violence) to pinpoint the impact of specific adverse events on HPA axis functioning, and therefore mental health conditions related to stress. Most studies of ACEs have focused on higher-income, well-educated populations, yet toxic stress tends to be embedded in social disadvantage and intergenerational adversity is often comorbid with other forms of maltreatment.[17]

Future research should centre on identifying potential moderators and mediators between ACEs and perceived stress and anxiety in order to create targeted interventions that support mental health among women who have experienced ACEs and reside in LMICs. For instance, social support, emotion regulation skills and positive self-perceptions are powerful protective factors that buffer women from the harmful effects of ACEs. In addition to exploring potential protective factors, it is important to investigate other unmeasured moderators, mediators and confounders impacting the relationship between ACEs and mental health. Furthermore, it would be insightful to disentangle the interplay among ACEs, adult stress and anxiety, and adult stress system functioning, which are not well understood in LMICs and has not been deeply explored in South Asia specifically.[5 90 91] Stress, anxiety and cortisol are highly correlated as individuals who experience high anxiety, or clinically significant GAD, may be more likely to report higher levels of perceived stress. Exploring how this leads to or is caused by altered cortisol levels would be beneficial to inform intervention and policy, which also requires an understanding of protective, buffering factors that mitigate the consequences of ACEs at the individual, household and community levels. This is especially relevant as ACEs have been found to be predictive on a population level rather than on an individual level.[92] Interventions targeting girls within community or school settings that harness these protective factors and prevent the consequences of ACEs have the potential to lessen HPA axis hyperactivity, prevent the intergenerational transmission of adversity and improve mental health outcomes in this population. As this study implies, understanding the differential impact of specific ACEs on perceived stress, anxiety and HPA-axis functioning can provide the foundation to then work on re-appraising traumatic experiences and reinforcing resilience.

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