

# PTSD symptoms and cortisol stress reactivity in adolescence: Findings from a high adversity cohort in South Africa

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## ABSTRACT

**Background:** Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is implicated in the pathophysiology of post-traumatic stress disorder (PTSD). However, there has been little study of HPA stress reactivity in association with PTSD symptoms (PTSS) in children; and there is limited research on PTSD in low and middle-income countries, where trauma exposure is more common and co-occurring stressors more likely.

**Method:** We assessed the relationship between PTSS and cortisol stress reactivity in children aged 13 years ( $N = 291$ ) from an impoverished South African community. HPA axis stress reactivity was indexed by salivary cortisol during the Trier Social Stress Test (TSST).

**Results:** In regression analyses both trauma exposure and PTSS showed small inverse associations with total cortisol output (area under the curve with respect to ground) during the TSST, but PTSS effects did not withstand correction for covariates. In addition, hierarchical linear modelling (HLM) found that PTSS were associated with alterations in the shape of the profile of cortisol reactivity that were moderated by sex. In girls, PTSS were associated with reduced linear slope but larger quadratic slopes, whereas the opposite pattern was found in boys. Thus, elevated PTSS were associated with overall blunted profiles of cortisol stress reactivity in girls, but a larger quadratic slope in boys reflects a steeper cortisol increase and decline in boys. There was no relationship between trauma exposure (with or without PTSS) and cortisol reactivity profiles in HLM analyses.

**Conclusion:** In children from a high adversity, low and middle income country context, sex specific associations were found between PTSS and cortisol responses to psychosocial stress. Further research should probe HPA axis functioning more comprehensively in such populations to understand the biological associations of PTSS.

## 1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis plays a major role in the central nervous system response to stress (Teicher et al., 2002), and has been implicated in the development of stress related psychological disorders, including posttraumatic stress disorder (PTSD) (De Bellis and Zisk, 2014; Pan et al., 2018). Research in adults has found evidence of lower basal cortisol secretion in association with PTSD, though mixed

findings have been reported (De Bellis and Zisk, 2014; Pan et al., 2018). In contrast, studies of paediatric PTSD have more consistently demonstrated basal cortisol elevations (Carrión et al., 2002; De Bellis and Zisk, 2014; Delahanty et al., 2000; Fries et al., 2005). It has been argued that such discrepancies may reflect long term biological adaptation to stress, with prolonged periods of HPA hyperactivation following trauma ultimately being followed by “attenuation,” due to reduced biosynthesis of hormones, downregulation of pituitary glucocorticoid receptors, and/or

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increased receptor negative feedback sensitivity (Fries et al., 2005). The resultant corticosteroid hyposecretion is proposed to prevent potentially deleterious effects of prolonged cortisol elevation on neural and cardiometabolic functioning (Fries et al., 2005; McEwen, 1998). In support of this hypothesis, a meta-analysis has found that basal cortisol is inversely correlated with time since trauma in adults with PTSD (Carrión et al., 2002; Miller et al., 2007), and there is preliminary cross-sectional evidence that equivalent effects may be present in child and young people (Weems and Carrión, 2007).

In contrast to the relatively comprehensive study of basal cortisol, there has been much less attention to cortisol stress reactivity in the PTSD field. Cortisol reactivity to stress is argued to better reflect psychopathological processes than baseline cortisol levels and is particularly relevant in the context of stress related disorders (Zorn et al., 2017). Studies that measure cortisol responses to a stress challenge in relation to adult PTSD are limited and have yielded inconsistent findings (De Bellis and Zisk, 2014; Li and Seng, 2018; Schalinski et al., 2015). Importantly, there has been little investigation of HPA axis reactivity in children and adolescents with PTSD. One study of 124 violence-exposed children (Peckins et al., 2012) found that while violence exposure was associated with lower cortisol reactivity in response to the Trier Social Stress Test (TSST) in boys (but not girls), there was no evidence of associations between PTSD symptoms (PTSS) and cortisol response. However, levels of PTSS were extremely low in this USA sample. A second study found evidence of blunted cortisol reactivity in maltreated adolescent girls ( $n = 67$ ) compared to a control group ( $n = 25$ ), but no effect of the presence of current PTSS in this association (MacMillan et al., 2009a). However, only 19 % of the sample reported any current PTSS. Given the potential importance of childhood stressors in the development of the HPA axis, further examination of whether childhood PTSD is linked to cortisol reactivity is warranted, particularly in contexts of heightened trauma exposure or in clinical populations with paediatric PTSD.

In addition to the general lack of research focus on child cortisol stress reactivity in association with PTSD, it is striking that the available evidence derives almost exclusively from high-income country populations. In low and middle income countries (LMICs) childhood trauma exposure is higher (Atwoli et al., 2015), and occurs against a backdrop of prevailing adversity, which may modulate stress-related biological systems (McDade et al., 2013), including HPA axis activity (Flinn and England, 1997). Consequently, findings to date may not generalise to contexts with a high prevalence of trauma and stress (Atwoli et al., 2015).

We examined associations between PTSS and HPA cortisol reactivity in young people (13-years) living in the township of Khayelitsha, an impoverished peri-urban settlement on the outskirts of Cape Town, South Africa, where rates of child trauma exposure are markedly high (Gregorowski and Seedat, 2013). We tested the hypothesis that PTSS would be associated with cortisol reactivity using a controlled social stressor—the TSST – at 13 years old. Based on the limited available evidence, blunted cortisol stress reactivity in children with higher PTSS was predicted. Sex was included as a potential moderator of this relationship, given preliminary evidence of sex differences in the cortisol response in the context of trauma (Bouma et al., 2009; Takai et al., 2007), and meta-analytic evidence that depression/anxiety disorder related alterations in cortisol reactivity are moderated by sex, with women showing blunted but men elevated reactivity compared to controls (Zorn et al., 2017). We also examined whether the extent of trauma exposure could explain any associations between PTSS and cortisol reactivity.

## 2. Methods and materials

### 2.1. Participants

From 1999–2003 a randomised controlled trial was conducted in a socio-economically disadvantaged South African peri-urban settlement

near Cape Town (Khayelitsha). A total of 449 pregnant women were randomised to a 16-session perinatal psychosocial intervention or control group. The intervention included home visits to mothers by lay community workers, which aimed to support their parenting. The intervention improved maternal sensitivity and caregiver child attachment (Cooper et al., 2009). At child age 13 years, study dyads from both control and intervention groups were re-invited to attend an assessment clinic. Twenty-four children had died since the original randomisation process. Of the remaining 425, 333 were able to travel to the assessment centre, which was necessary to provide cortisol measures. Wherever possible, the team arranged for these child and mother participants to travel to Cape Town for their study assessments. Of these, 15 were excluded due to asthma steroid pump use, which can interfere with cortisol measurements, 14 were lost due to issues with labelling and storing the samples, 3 were missing PTSS data and 10 had missing data on covariates, resulting in a final sample of 291 adolescents for the current study.

### 2.2. Measures

#### 2.2.1. PTSD

The Child PTSD checklist (Amaya-Jackson et al., 1995) was completed at the 13-year research assessment. This is a 28-item self-report scale assessing the presence of 17 DSM-IV PTSD symptoms over the past month with regard to the most upsetting traumatic experience a child has had. Each item was scored based on a 3-point Likert-scale, 0 = Never, 1 = Some days, 2 = Every Day and a total PTSS sum score computed. This scale has been used widely in the South-African context, and with native isiXhosa speakers such as those living in Khayelitsha (Cluver et al., 2009; Suliman et al., 2009), and has good internal validity, reliability and discriminant abilities (Boyce et al., 2012). As standard for the scale, adolescents were asked to think of the most frightening event that had happened to them and keep this in mind while responding to the questions.

#### 2.2.2. Cortisol Reactivity: TSST

Adolescents completed the TSST in line with standard protocols (Kirschbaum et al., 1993). Following a baseline saliva sample, participants were given 3 min to prepare a 5-minute speech on anything about themselves, to be delivered to an audience. They were then led to a second room where they gave their 5-minute speech to two ‘examiners’ in white coats in front of a camera, with a 24-inch monitor displaying the image of the participants that was captured. Following the speech, examiners administered a serial sevens subtraction task for 4 min. Upon completion, the participant returned to the first room where a post-stressor saliva sample was collected. Subsequent saliva samples were collected at +10, +20, +30, +40 and +50 min, while participants completed a structured, neutral interview unrelated to the task. The seven pre-labelled salivapots were stored in a deep freeze ( $-4^{\circ}\text{C}$ ) until they were shipped on dry ice to a lab in Germany for cortisol assay. Five individual observations (not whole cases) were excluded as biologically implausible due to extremely high readings, which typically occurs due to contamination with blood in the saliva.

We calculated area under the curve with respect to ground (AUCg) of cortisol concentrations, as a measure of total cortisol secretion during the task. The trapezoid method was used to calculate AUCg across the seven cortisol measurements using the trapezoid method, following standard formula (Pruessner et al., 2003):

$$\text{AUCg} = \sum I = \ln -1(m_{(i+1)} + m_i) \cdot t_i$$

with  $t_i$  denoting the individual time distance between measurements,  $m_i$  the individual measurement, and  $n$  the total amount of measures.

#### 2.2.3. Trauma exposure

Trauma exposure was assessed using the child exposure to community violence checklist (CECV). Adolescents reported exposure to

different types of community and household violence on an adapted version of the CECV with 23-items (Cluver et al., 2007). The frequency of exposure was rated on a 3-point Likert scale: 0 = Never, 1 = A few times, 2 = Many times. This version of the measure has previously been used to index extent of trauma exposure among adolescents in South African townships, and total scores capture overall exposure to particularly common traumatic experiences in those communities, including robbery, assault, stabbings or shootings in the community, or domestic violence and abuse at home (Boyes et al., 2012; Cluver et al., 2009). The measure has previously been found to be reliable and valid in a South African context (Martin et al., 2013); showing good internal consistency ( $\alpha = 0.89$ ) and it is associated ( $r = 0.50$ ) with adolescent PTSS (Boyes et al., 2012).

#### 2.2.4. Measurement of key covariates

During the 13-year clinic visit, participants' weight and height were measured to calculate BMI ( $\text{kg}/\text{m}^2$ ). A categorical measure of cumulative contextual adversity was used to reflect socioeconomic status. Using data completed by the child's carer and the child at 13 years old, the following variables were coded as 0 = Present or 1 = Absent: overcrowding (number of people dwelling in the household reported by carer, above or below highest quintile), primary caregiver unemployed, primary caregiver only has primary-level education, house lacks running water/toilet/electricity, family members have gone without food for a whole day in the last week, relationship breakup with partner or husband, partner has been violent toward mother/caregiver. The average of these indicators was taken for each child, resulting in a score from 0 to 1 for each child, where 1 reflects lowest level of adversity.

#### 2.3. Data analysis

Multiple regression analyses were used to investigate associations between cortisol AUCg and PTSS, with PTSS as the independent variables and cortisol AUCg as the dependent variable. We also assessed the relationship between cortisol AUCg and trauma exposure (versus PTSS) using regression. In both these analyses, we tested for potential moderation of associations by sex.

Subsequent analyses were conducted using the MIXED procedure in STATA version 15. Cortisol reactivity over the TSST was analysed using two-level hierarchical linear modelling (HLM). First, we estimated individual variance in baseline levels and the trajectory of cortisol concentration over time (level 1) using linear, quadratic and cubic terms, as reported previously (Fearon et al., 2017). Random effects for both constant and slopes were included in all models.

Hypothesis testing was then carried out by including between-subjects (level 2) predictors in the model. In an analysis to test for the effect of PTSS scores on cortisol reactivity to stress, we ran a HLM model examining PTSS, sex, and the sex  $\times$  PTSS interaction in relation to the cortisol intercept and linear and quadratic slopes, and we additionally ran an equivalent model to test for potential effects of trauma exposure, with CECV scores replacing the PTSS term. We tested for effect modification by sex in all analyses. Where interaction effects were identified, we conducted further exploration using tests of simple slopes, and illustrated findings via plots of estimated marginal means (i.e., model-based predictions).

We initially ran all analyses including intervention group status (coded as 0 = no intervention and 1 = perinatal intervention), cumulative contextual adversity and BMI as covariates. However, we were missing BMI data for a number of participants ( $n = 23$ ). BMI showed no associations with outcome in any model, and findings were identical when we reran analyses without adjusting for BMI. Therefore, in the final models reported we adjusted for intervention group and adversity, but not for BMI.

### 3. Results

#### 3.1. Participant information

The final sample of 291 adolescents comprised 146 girls and 144 boys aged 13 years with an average BMI of  $2.32 \pm 4.9 \text{ kg}/\text{m}^2$ . Adolescents reported, on average, being exposed to 4.9 different types of trauma on the CECV. PTSS scores on the Child PTSD Checklist ranged from 0 to 36 ( $M = 9.2 \pm 8.3$ ). As expected, PTSS were positively correlated with trauma exposure ( $r = 0.41, p < 0.001$ ) and contextual adversity ( $r = 0.17, p = 0.01$ ).

#### 3.2. Cortisol AUCg

There was limited evidence for an association between cortisol AUCg and PTSS. In unadjusted regression analyses, a small inverse association was identified between PTSS and cortisol AUCg ( $B = -0.059, 95\% \text{ CI } -0.118, -0.001, p = .046; R^2 = 0.013, F_{1,292} = 3.97, p = 0.047$ ). However, this effect was no longer statistically significant ( $B = -0.059, 95\% \text{ CI } -0.116, 0.003, p = .061$ ) when child sex ( $B = -0.183, 95\% \text{ CI } -1.17, 0.801, p = .71$ ), contextual adversity ( $B = -0.696, 95\% \text{ CI } -3.42, 2.03, p = .62$ ), and perinatal intervention status ( $B = -0.080, 95\% \text{ CI } -1.06, 0.905, p = .87$ ) were included in the model ( $R^2 = 0.015, F_{4,289} = 1.09, p = 0.36$ ). Further inclusion of a PTSS by sex interaction in the model yielded no evidence of moderation by sex ( $B = 0.026, 95\% \text{ CI } -0.94, 0.145, p = .67; R^2 = 0.15, F_{5,288} = 0.90, p = 0.48$ ).

When we ran equivalent analyses examining trauma exposure (measured by the CECV) instead of PTSS scores as the predictor the results were similar. An small, inverse association was present between trauma exposure and cortisol AUCg in unadjusted analyses ( $B = -0.126, 95\% \text{ CI } -0.184, -0.009, p = .031; R^2 = 0.016, F_{1,292} = 4.71, p = 0.031$ ), and this effect was retained once covariates were included in the model ( $B = -0.097, 95\% \text{ CI } -0.188, -0.006, p = .037; R^2 = 0.018, F_{4,289} = 1.30, p = 0.270$ ). There was no evidence of a trauma exposure by sex interaction in the prediction of cortisol AUCg ( $B = -0.025, 95\% \text{ CI } -0.107, 0.057, p = .56; R^2 = 0.018, F_{5,288} = 1.11, p = 0.36$ ).

#### 3.3. HLM: cortisol change over time

First, HLM analysis was used to establish linear, quadratic and cubic functions of time cortisol reactivity over time, as previously reported for this sample (Fearon et al., 2017). Summary statistics are shown in Table 1. As expected, the change in cortisol over time was curvilinear, with a peak at +10 to +20 min post-stressor (see Fig. 1); and there was evidence for linear, quadratic and cubic slopes: linear  $B = 0.97, p < 0.001; 95\% \text{ CI } [0.75, 1.18]$ ; quadratic  $B = -0.22, p < 0.001; 95\% \text{ CI } [-0.27, -0.18]$ ; cubic  $B = 0.02, p < 0.001; 95\% \text{ CI } [0.01, 0.02]$ .

#### 3.4. HLM: Effects of PTSS on cortisol change over time

Next, PTSS, sex and PTSS  $\times$  sex interactions were included in the model, to examine associations with cortisol intercept and change over time. Results are presented in Table 2, Model 1. PTSS were not

**Table 1**  
Summary statistics for salivary cortisol concentration by sex.

Time Point	Boys		Girls	
	Mean ( $\mu\text{g}/\text{dL}$ ) $\pm$ SD	N	Mean ( $\mu\text{g}/\text{dL}$ ) $\pm$ S D	N
Baseline (no stress)	2.89 $\pm$ 0.91	149	2.50 $\pm$ 0.86	152
Post-test (stress)	3.36 $\pm$ 0.83	148	3.38 $\pm$ 0.83	152
+10 min	3.67 $\pm$ 0.79	147	3.70 $\pm$ 0.77	153
+20 min	3.67 $\pm$ 0.85	148	3.55 $\pm$ 0.79	153
+30 min	3.50 $\pm$ 0.77	149	3.43 $\pm$ 0.80	153
+40 min	3.27 $\pm$ 0.78	149	3.34 $\pm$ 0.79	153
+ 50 min	3.23 $\pm$ 0.83	148	3.18 $\pm$ 0.78	151

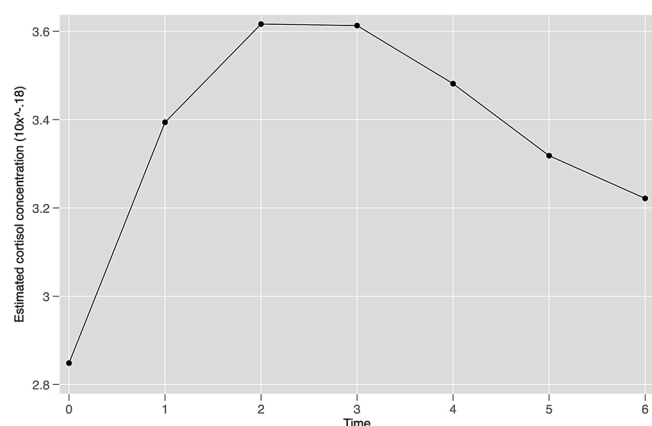


Fig. 1. Estimated cortisol concentrations as a function of PTSS and sex.

significant predictor of the cortisol intercept ( $B = -0.42$ ,  $p = 0.060$ , 95 % CI  $[-0.85, 0.02]$ ). There was evidence for effects of PTSS on the linear and quadratic slopes of the cortisol curves, and these were moderated by sex  $\times$  PTSS interactions (Table 2, Model 1). In girls, PTSS were weakly negatively associated with the linear ( $B = -0.07$ ,  $p = 0.043$ , 95 % CI  $[-0.13, -0.002]$ ) cortisol slope, and positively associated with the quadratic ( $B = 0.01$ ,  $p = 0.017$ , 95 % CI  $[0.002, 0.02]$ ) cortisol slope for reactivity over time. Thus, the overall pattern was one of weaker increase coupled with a shallower curve, resulting in overall blunted reactivity. By contrast, in boys, PTSS were positively associated with the linear slope ( $B = 0.07$ ,  $p = 0.038$ , 95 % CI  $[0.01, 0.14]$ ) and negatively associated with the quadratic slope ( $B = -0.01$ ,  $p = 0.016$ , 95 % CI  $[-0.02, -0.002]$ ) for cortisol change over time. Thus, PTSS in boys was associated with a larger quadratic slope, which reflects a greater cortisol increase and decline. Fig. 2 presents the model-based predicted cortisol concentration for boys and girls separately, with cortisol concentration estimated for scores 1 SD above and below the mean of the PTSS scores, for visual purposes (note that as the figure is based on a cut-off versus continuous scores it does not precisely duplicate model based findings). There were no effects of additional covariates, intervention group status

( $B = -0.03$ ,  $p = 0.34$ , 95 % CI  $[-0.20, 0.14]$ ) or cumulative contextual adversity ( $B = -0.23$ ,  $p = 0.75$ , 95 % CI  $[-0.71, 0.24]$ ), on associations between PTSS and cortisol reactivity.

### 3.5. HLM: Effects of trauma exposure on cortisol change over time

Next, we re-ran our models, replacing PTSS scores with extent of trauma exposure (CECV scores), including sex  $\times$  trauma exposure interactions. These analyses revealed no effects of trauma exposure (as main effect or in interaction with gender) on the intercept, linear or quadratic slopes. Findings are presented in Table 2, Model 2. There were again also no effects of additional covariates, intervention group status ( $B = -0.04$ ,  $p = 0.68$ , 95 % CI  $[-0.21, 0.13]$ ) or cumulative contextual adversity ( $B = -0.12$ ,  $p = 0.64$ , 95 % CI  $[-0.61, 0.38]$ ) in the model.

## 4. Discussion

In adolescents from a deprived LMIC context, we found a complex pattern of associations between symptoms of PTSD and cortisol reactivity to psychosocial stress. First, there was tentative evidence that both extent of trauma exposure and PTSS were associated with lower overall cortisol output (AUCg) during the TSST. These effects were small in magnitude and the association with PTSS did not survive correction for covariates. Second, we found evidence that PTSS could predict trajectories of cortisol secretion over the course of the TSST, but these effects were moderated by child sex. Specifically, girls with high levels of PTSS showed a shallower cortisol response to the TSST compared those with fewer symptoms, whereas for boys, posttraumatic distress was associated with a relatively strong post-stressor cortisol increase and recovery. While PTSS in boys was associated with a relatively 'normal' profile of cortisol reactivity, the high PTSS boys have a larger quadratic slope which reflects their steeper cortisol increase and decline. In contrast, we found no evidence that extent of trauma exposure was associated with profiles of cortisol reactivity in our sample.

In adults, PTSD has been associated with both hyper (Elzinga et al., 2003; Zaba et al., 2015) and hypo-reactivity cortisol to stress (Wichmann et al., 2017; Zaba et al., 2015), while others have found no association (Bremner et al., 2003; Roelofs et al., 2009; Simeon et al., 2007). There has been extremely limited prior investigation of cortisol stress reactivity in association with child PTSD. In the current study, we found only tentative evidence that PTSS are associated with overall reduced cortisol output in response to stress, as indexed by AUCg. This effect was small in magnitude, not sex specific, and did not survive correction for covariates. In addition, extent of trauma exposure similarly was inversely associated with cortisol AUCg, suggesting that this effect is not particularly specific to the presence of PTSS but may also occur in response to trauma exposure per se.

By contrast, when we examined trajectories of cortisol reactivity over the course of the TSST, a more subtle picture of sex specific effects in the relationship between PTSS and HPA axis activity in children emerged. The pattern of results for males could be interpreted to suggest that PTSS was associated with heightened cortisol reactivity to the stressor in this group. Why males and females might have a seemingly opposite pattern of response is unclear, although more generally there is consistent evidence of differential HPA function in males and females (Heck and Handa, 2019; Zorn et al., 2017). Also, it is important to note that one could interpret the heightened cortisol response and recovery as representing a more optimal cortisol response in males with higher PTSS, because a strong phasic response in the HPA axis could imply better cortisol regulation. Such a pattern could indicate an adaptive response to chronic stress.

Our observations of enhanced cortisol reactivity and recovery in association with PTSS in boys, versus a blunted stress response in girls, are consistent with observations of equivalent sex differences in cortisol secretion in the context of anxiety/depression, where males have been found to show increased reactivity and females blunted reactivity

Table 2

HLM growth curve analysis of cortisol response in relation to PTSS, by sex (Model 1) and trauma exposure, by sex (Model 2). Male sex is reference category ( $N = 291$ ).

	Intercept		Linear slope		Quadratic slope	
	B (95 % CI)	p	B (95 % CI)	p	B (95 % CI)	p
Model 1						
PTSS	-0.42 (-0.85, -0.02)	.060	0.22 (0.06, 0.37)	.007	-0.03 (-0.05, -0.01)	.001
Sex	-0.26 (-0.57, 0.05)	.119	0.18 (0.06, 0.30)	.003	-0.03 (-0.04, -0.01)	.000
Sex $\times$ PTSS	0.20 (-0.06, 0.48)	.135	-0.14 (-0.24, -0.05)	.004	0.02 (0.01, 0.03)	.001
Model 2						
Trauma exposure	-0.06 (-0.67, 0.56)	.855	0.05 (-0.17, 0.27)	.653	-0.01 (-0.03, 0.02)	.550
Sex	-0.03 (-0.37, 0.31)	.883	0.07 (-0.06, 0.19)	.286	-0.01 (-0.02, 0.01)	.178
Sex $\times$ exposure	-0.13 (-0.52, 0.27)	.529	-0.03 (-0.17, 0.12)	.719	0.01 (-0.01, 0.02)	.571

PTSS: Posttraumatic Stress Symptoms.

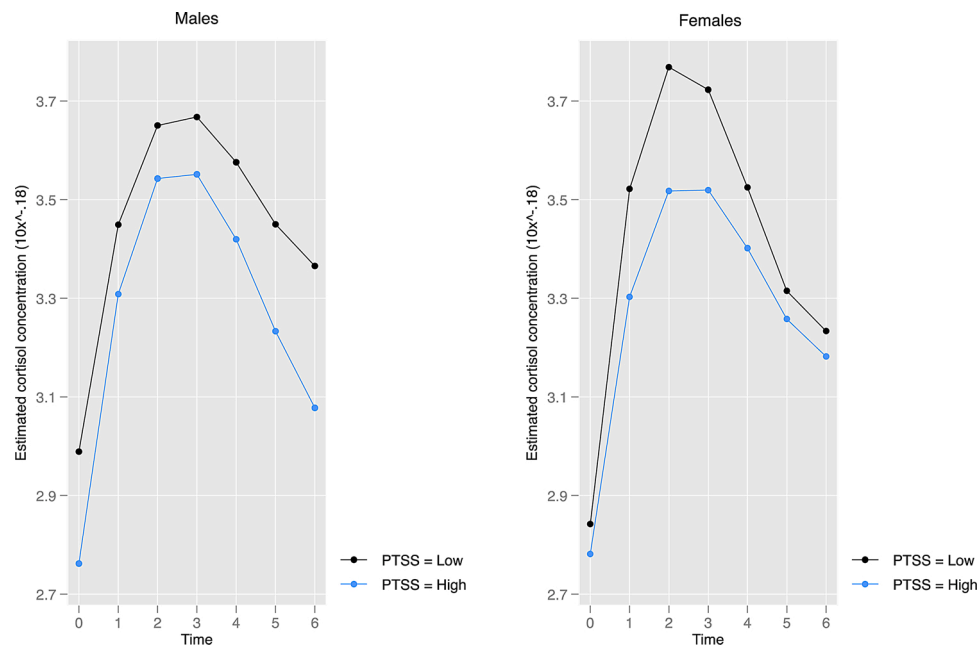


Fig. 2. Estimated cortisol concentrations as a function of PTSS and sex.

compared to their control group counterparts (Zorn et al., 2017). However, these findings must also be considered in the light of the overall trend being one of reduced cortisol output in the context of PTSS. Thus, even in boys PTSS were not associated with greater cortisol output overall, despite the evidence for a steeper cortisol increase and recovery. The current evidence, deriving from a group of young people experiencing high levels of co-occurring adversity, contrasts with previous studies that have failed to identify PTSD effects on HPA reactivity in adolescents (MacMillan et al., 2009a; Peckins et al., 2012). Previous null findings have derived from samples in which the levels of PTSD symptoms are extremely low, which may explain the discrepancy. Prior studies have also tended to look only at indices of cortisol output, versus patterns of change over time in response to stress, and our findings suggest it is particularly important to include investigation of the latter. However, further examination of high-adversity populations of young people is warranted, particularly considering that the HPA axis activity may be sensitive to context levels of threat (Giudice et al., 2011).

The neurobiological underpinnings of sex differences in HPA axis reactivity remain poorly understood (Zorn et al., 2017), as do the reasons for increased vulnerability to PTSD in girls versus boys that emerges during adolescence (Haag et al., 2019). Previous work with South African youth has highlighted problems with aggression and externalising symptoms in trauma exposed boys, whereas girls may be vulnerable to depression (du Plessis et al., 2015). This is consistent with some evidence of sex differences in the adult presentation of PTSD, where higher levels of irritability and anger in males have particularly been reported (Green, 2003). Exploration of potentially varied clinical presentations of PTSD in relation to cortisol reactivity could further our understanding of sex differences. Importantly, our findings highlight the critical importance of taking account of sex differences in analyses in this context.

We did not find evidence of an effect of trauma exposure on profiles of cortisol reactivity over time in our sample, which suggests that the sex specific HPA axis alterations observed are particular to the presence of PTSS, versus being a consequence of exposure to trauma per se. By contrast, when we looked at cortisol output overall, we found that trauma exposure as well as levels of PTSS tended to be inversely associated with cortisol AUC<sub>G</sub> during the TSST. This is consistent with some previous evidence that trauma exposure is associated with blunted cortisol secretion in response to stress in adolescents (MacMillan et al., 2009b), although evidence of elevated reactivity has also been found in

this population (Rao et al., 2008). Discrepant findings may be explained by differences across studies in the type of trauma measured, whether the trauma is a single-event or repeated, and the time between trauma exposure and measurement of cortisol reactivity. Future studies should look to tease apart the effects of PTSS and trauma exposure on cortisol and HPA dysregulation. Importantly, more research is required in LMIC contexts, where trauma exposure is extremely prevalent and may be more normative (Atwoli et al., 2015).

Findings should be considered in the light of several limitations. Our data are cross-sectional and correlational, so causal relationships cannot be inferred. Plausibly, altered cortisol responses may be linked with the expression of PTSS, or may represent a psychobiological vulnerability, with some evidence suggesting that that traumatised individuals with a blunted cortisol response to stress could be more susceptible to developing PTSD (Delahanty et al., 2000; McFarlane et al., 1997). Cross-lagged longitudinal studies and experimental trials are required to understand the causal direction of this association. In addition, the stress task was artificial, and thus the cortisol response may not be generalizable to real world stressful situations, or non-social stress.

#### 4.1. Conclusion

Few previous studies have assessed cortisol reactivity in children with PTSS, and none have done so in LMIC contexts. We provide evidence that the cortisol response to stress is altered in children with PTSS, and that such changes are sex specific. The findings require replication to establish the causality of the relationship, though they suggest that PTSS impairs cortisol reactivity, which can impact the stress response system in later life.

#### Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

#### Declaration of Competing Interest

The authors report no declarations of interest.

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