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Hair cortisol concentrations in war-affected adolescents: A prospective intervention trial

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ABSTRACT

Temporal examinations of the biological signature of stress or trauma in war-affected populations are seldom undertaken. Moreover, few studies have examined whether stress biomarkers track biological sensitivity to brief interventions targeting the improvement of psychosocial wellbeing. Our study is the first to prospectively examine, in war-affected adolescents, the associations between hair cortisol concentrations (HCC) and self-reports of stress, insecurity, posttraumatic reactions, and lifetime trauma. We conducted a randomized controlled trial to test the impact of an 8-week intervention based on profound stress attunement. We collected data for a gender-balanced sample of 733 Syrian refugee (n = 411) and Jordanian non-refugee (n = 322) adolescents (12–18 years), at three time-points. We used growth mixture models to classify cortisol trajectories, and growth models to evaluate intervention impact on stress physiology. We observed three trajectories of HCC: hypersecretion, medium secretion, and hyposecretion (9.6%, 87.5% and 2.9% of the cohort, respectively). For every one percent increase in levels of insecurity, adolescents were 0.02 times more likely to have a trajectory of hypersecretion (95% CI: 1.00, 1.03, p = 0.01). For each additional symptom of posttraumatic stress reported, they were 0.07 times less likely to show hyposecretion (95% CI: 0.89, 0.98, p = 0.01). Indeed, stronger posttraumatic stress reactions were associated with a pattern of within-individual cortisol dysregulation and medium secretion. Overall, HCC decreased by a third in response to the intervention (95% CI: −0.19, −0.03, p = 0.01). While the intervention decreased HCC for youth with hypersecretion and medium secretion, it increased HCC for youth with hyposecretion (95% CI: 0.22, 1.16, p = 0.004), relative to controls. This suggests a beneficial regularization of cortisol levels, corroborating self-reports of improved psychosocial wellbeing. We did not find evidence to suggest that gender, resilience, or posttraumatic stress disorder influenced the strength or direction of responses to the intervention. This robust impact evaluation exemplifies the utility of biomarkers for tracking physiological changes in response to interventions over time. It enhances the understanding of trajectories of endocrine response in adverse environments and patterns of stress responsivity to ecological improvement.

1. Introduction

The use of biomarkers such as hair cortisol is at the forefront of chronic stress research (Russell et al., 2012; Steudte-Schmiedgen et al., 2016; Stalder et al., 2017). Stress biomarkers have the potential to provide a biological signature of adverse experiences, offering a window into the developmental and neuroendocrinological impacts of past and current adversity. To-date, few studies have robustly examined trajectories of cortisol production in populations affected by war and forced displacement. Psychoendocrinological research with active

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combatants and/or victims of war has measured salivary cortisol levels as a means to evaluate wartime stress and posttraumatic stress disorder (PTSD). This pioneering body of work includes a cross-sectional study of 20 Gulf War veterans with and without PTSD (Yehuda et al., 2010), a study of cortisol and immune responses of 20 male patients from the Iran-Iraq war (Masoudzadeh et al., 2012), an experimental study with 240 Chinese soldiers before and after high-intensity military operations (Li et al., 2012), and a prospective study of 30 refugees to Germany examining how victims of rape responded to trauma reminders (Gola et al., 2012). Other studies have examined hair cortisol concentration (HCC) as an index of chronic stress in war-affected civilian populations. One compared 10 adults with PTSD and 17 war-affected controls in a camp for internally-displaced people in northern Uganda (Steudte et al., 2011). A second examined 39 female university students after the 2011 Libyan war (Etwel et al., 2014). Much of this work has been cross-sectional and included relatively small samples of adult men and women, limiting the ability to examine differential cortisol trajectories over time in response to past trauma and/or current stressors.

The literature reports inconsistent associations between trauma exposure and changes in cortisol secretion (Steudte-Schmiedgen et al., 2016). While some studies show that trauma-exposed individuals have attenuated cortisol levels, other research – with participants experiencing ongoing stressors – suggests that continued exposure to adverse experiences can lead to cortisol hypersecretion (Miller et al., 2007; Mewes et al., 2017; Stalder et al., 2017). In a recent review of the hair cortisol literature, Steudte-Schmiedgen et al. (2016) suggested that trauma experiences may induce an initial up-regulation of cortisol secretion, followed by attenuation of cortisol production with additional trauma, with or without posttraumatic disorder.

There is also good evidence that recent stressors increase hypothalamic-pituitary-adrenal (HPA) activity, but that chronic, ongoing stress may ultimately lead to cortisol hyposecretion (Miller et al., 2007). A cross-sectional study of adults observed elevated HCC in 56 male and female, recent asylum seekers to Germany, relative to 24 permanently-settled male Turkish immigrants and 28 male German hosts (Mewes et al., 2017). However, the Turkish immigrants showed relative hypocortisolism by comparison to the host community. The observation that recent asylum seekers had higher HCC and settled Turkish immigrants had lower HCC relative to German hosts, was interpreted to reflect the impacts of insecure living conditions and continued stresses over an extended period, with cortisol down-regulation over time. PTSD status had no impact on cortisol concentrations. By contrast, a case-control study with 64 female adolescents (12–15 years old) found that, while HCC were elevated 7 months after experiencing the 2008 Wenchuan earthquake, the group of students with PTSD showed a pattern of blunted cortisol reactivity, suggesting attenuated HCC production (Luo et al., 2012). The patterns of associations between PTSD symptoms and cortisol production in children and adolescents are certainly complex (Russell et al., 2017).

While trauma and stress exposures are associated with altered cortisol production, clear interpretation of findings is confounded by differences in the number of lifetime trauma and in the severity of concurrent stressors. Thus, how the combination of significant lifetime trauma exposure (such as that experienced during war and forced displacement) and exposure to everyday stressors (such as that experienced during the process of resettlement) might affect the developmental HPA responses remains unclear. In the wake of war, civilian populations assume the heavy burden of violence, loss, and trauma, as well as ongoing stress, fear, and insecurity (Miller and Rasmussen, 2010). Yet sizeable proportions of war-affected and refugee people, whether children or adults, show remarkable functioning, indicating the presence of multiple risk and resilience pathways in the wake of war (Tol et al., 2011a,b; Tol et al., 2013; Hadfield et al., 2017). In terms of impacts on the body, important endocrine changes may result from these exposures to past trauma, ongoing stress, and resilience factors.

Extant studies of the biological stress response in war and disaster settings, however, rest largely upon observational or case-control studies, rather than discrete interventions. It is still an open question whether stress biomarkers might be used to track the impacts of interventions targeting improvements in mental health and psychosocial wellbeing in humanitarian crises. A small number of studies have used salivary cortisol as a measure of physiological stress to evaluate intervention impacts, such as poverty-alleviation programs in very low-income children in Mexico (Fernald and Gunnar, 2009), cash transfers among the poor (Haushofer and Shapiro, 2016), or increased access to health care (Haushofer et al., 2017). Cortisol levels in blood, saliva, or urine are useful for measuring stress reactivity, but highly sensitive to the circadian rhythm of cortisol production and other confounders (Russell et al., 2012). By contrast, HCC acts as a 'chronic stress diary,' providing a long-term marker of the endocrine stress response and a useful measure of integrated HPA activity, pre- and post-intervention. To our knowledge, ours is the first study to use HCC to evaluate the benefits and/or differential impacts of an intervention in communities affected by war and forced displacement. It is also one of the first to prospectively examine trajectories of adolescent cortisol production.

Some studies have focused attention on the impacts of early childhood adversity by framing this issue in terms of 'toxic stress' (e.g. Shonkoff et al., 2012). Other studies have advanced an adaptive calibration model to highlight the sensitivity of allostatic load responses to variable environments (e.g. Del Giudice et al., 2011). The stress response system works as a mechanism of conditional adaptation, to coordinate physical and psychosocial challenges, to filter information from the environment, and to regulate a broad range of life history and developmental behaviors (Boyce and Ellis, 2005; Del Giudice et al., 2011, 2012; McEwen, 2012). Among children and adolescents specifically, the adaptive calibration model provides a framework for understanding the developmental trade-offs humans make for resource allocation under adversity, leading us to expect different biological responses to low, moderate, unpredictable, or severe ecological stress. Del Giudice et al. (2011) advanced four patterns of responsivity, characterised by sensitive, buffered, vigilant, and unemotional patterns of physiological stress profiles. Understanding both individual differences in stress physiology and individual differences in responsivity to interventions is important (Pluess and Belsky, 2013; Bakermans-Kranenburg and van IJzendoorn, 2015), in order to provide a better appreciation of who might benefit most from psychosocial interventions.

1.1. Context for this study

We aimed to understand patterns of cortisol production in youth who were differentially exposed to war-related trauma and forced displacement, and differentially engaged in a short, structured humanitarian intervention. In Jordan, Syrian refugee and host-community youth represent two cohorts with strikingly different exposures to trauma, stress, and insecurity (Panter-Brick et al., 2017a,b). Syrian refugees face the demands of adjustment to living in host communities following prolonged exposure to the toxic stress of insecurity, fear, and loss (Save The Children, 2017). As of October 2017, over 5.3 million people have been forced to leave Syria – this is the largest refugee crisis since the end of World War II; over 654,000 Syrians have taken refuge in Jordan, half of whom are children and adolescents under 18 years of age (United Nations High Commissioner for Refugees UNHCR, 2017). The large majority (79%) of Syrian refugees living in Jordan live side-by-side their Jordanian hosts, outside designated refugee camps (UNHCR, 2017). Jordanians are also deeply affected by the Syrian crisis, given increased pressures on neighboring countries to accommodate the very large influx of refugees (Mercy Corps, 2014); one in 15 people in Jordan is a Syrian refugee (UNHCR, 2017).

We partnered with Mercy Corps, a global humanitarian and development organization implementing an *Advancing Adolescents* programme informed by a profound stress attunement framework, in

Jordan, Lebanon, Iraq, Syria, and Turkey (Mercy Corps, 2014). The intervention explicitly teaches youth about the impacts of stress on the brain and seeks to enhance safety and psychosocial support while imparting life skills for groups of vulnerable 11–18 year-olds: the eight-week programme of group-based activities focuses on promoting a person's capacities for the mediation of extreme and prolonged stress (Mercy Corps, 2016; Macphail et al., 2017). Sessions are structured to teach stress attunement and skill acquisition, and involve a close mentorship with adult coaches, who are trained from the local community (Mercy Corps, 2014). Syrian refugees and Jordanian youth are brought together in small groups, for two sessions a week; boys and girls have separate sessions and coaches. Participants choose from a range of activities that include vocational skills (e.g. hairdressing), technical skills (e.g. computer repairs), fitness, or arts and crafts. In assessing programme impacts in Jordan using a randomized controlled trial study design, we found differential impacts across several mental health and psychosocial stress outcomes and for youth with low and high trauma exposures (Panter-Brick et al., 2017a). In the present paper, we specifically analyse hair cortisol as a marker of within- and between-person variation in adolescent responses to past trauma and current threats to wellbeing, in response to a brief intervention.

1.2. Research questions

Our study was guided by two main research questions. *First, is there heterogeneity in patterns of cortisol production among war-affected adolescents, and if so, what predicts this heterogeneity?* In line with previous research (Stalder et al., 2017), we expected to find several cortisol trajectories – for example, hypersecretion, normal secretion, and hyposecretion – that could be predicted by current stressors and/or past trauma exposures. On the basis of past studies, we hypothesized that current levels of human insecurity and/or perceived psychosocial stress would predict cortisol hyperproduction, while lifetime trauma exposure and/or posttraumatic stress reactions would predict some form of cortisol dysregulation, most likely reflected in hypoproduction.

Second, does engaging in a structured, psychosocial intervention change cortisol levels for adolescents over time, and if so, are there differential responses to the intervention? We hypothesized that stress biomarkers would track self-reports of psychosocial burden, as measured by insecurity, perceived stress, and posttraumatic stress, in terms of the biological signature of a profound stress attunement intervention. We also tested the model of adaptive stress calibration, examining whether some adolescents might be more responsive to the intervention because they are more sensitive or vigilant to their environments. This model suggests that patterns of unemotional, vigilant, buffered, and/or sensitive responses arise when individuals attune their physiology to the severity of contextual stressors, a calibration potentially influenced by trauma exposure, gender and other relevant life history variables (Del Giudice et al., 2011). We hypothesized that adolescents who had developed PTSD after significant trauma exposure were likely to be hypervigilant to their surroundings. Based on this, we expected that young people with PTSD would have a stronger HCC response to the psychosocial intervention, relative to those who did not develop PTSD in response to significant trauma exposure.

2. Methods

The study was conducted in four urban centers in northern Jordan, where Mercy Corps implemented programming for youth heavily affected by the Syrian crisis. Data were collected over three time-points: at baseline before the start of the psychosocial intervention (T1), at 2.8 months to capture the end of the 8-week intervention (T2), and at 11.3 months to capture a longer-term follow-up (T3). In this paper, we focus on the 733 adolescents for whom cortisol data were available for at least one time-point; we exclude 86 adolescents with missing physiological data (due to insufficient amount of hair). The full cohort (n = 817) is a representative sample of adolescents enrolled in Mercy Corps programming at the time of study (spring-winter 2015), including those engaged in the intervention and those wait-listed for future programme cycle implementation. Mercy Corps enrolled young people from the general population, on the basis of poor mental health and/or poor access to basic services. Our sample included Syrian refugees – living in Jordan for an average of nearly 3 years at baseline – and Jordanians living in the same communities, both eligible for the Mercy Corps programme.

The study received formal approval from the Prime Minister's Office of Jordan and ethics approval from Yale University. We conducted a randomized control trial (ClinicalTrials.gov ID: NCT03012451) to evaluate the *Advancing Adolescents* programme for impacts in the treatment group, relative to wait-listed controls. Written informed consent was obtained from community leaders, parents, and adolescents. Engagement with the community was very high: fewer than 30 families declined survey participation. Neither the sponsor (Elrha's Research for Health in Humanitarian Crises programme) nor Mercy Corps had a role in the design or conduct of data collection or analysis.

We recruited and trained a core team of Syrian/Jordanian fieldworkers to complete survey and biomarker data collection; 8 fieldworkers conducted face-to-face interviews and 4 supervisors checked data and stored samples on a daily basis. To respect local customs requiring that males do not talk to girls in private, all but two interviewers were female. Hair sample collection was done by professional (male and female) hairdressers in gender-separated spaces.

2.1. Measures

2.1.1. Socio-demographic data, lifetime trauma exposure, and resources for resilience

Standard socio-demographic data included displacement history, household wealth, and education. Lifetime trauma events were assessed with a Trauma Event Checklist, adapted from the Harvard Trauma Questionnaire and the Gaza Traumatic Event Checklist (Panter-Brick et al., 2009). The Checklist asks: *For each event described, please answer whether or not the event has happened to you personally, during your lifetime,* and features yes/no responses to 21 trauma items, including items such as: *Directly witnessed bombardment or rocket explosions as a result of war*; *Seen someone else severely beaten, shot or killed*; *Had your life in danger*; and *Been expelled from your home*. Resilience was measured through a 12-item, Arabic version of the Child and Youth Resilience Measure (CYRM), which measures individual, relational, and contextual resilience resources (Ungar and Liebenberg, 2011; Panter-Brick et al., 2017b).

2.1.2. Insecurity, stress, and posttraumatic stress symptoms

We used three main screening instruments previously used with war-affected adolescents and validated in the region, and confirmed instrument reliability in test-retest data (n = 41) and internal consistency with Cronbach's α (Panter-Brick et al., 2017a,b). We implemented the Human Insecurity (HI) scale, developed and validated in the West Bank with Palestinian populations to capture feelings akin to fear, rather than mere strain, in conflict-affected areas (Ziadni et al., 2011; Hamayel et al., 2014). It covers issues such as worries regarding inability to obtain daily life necessities, losing a source of income, fears about the future, and family safety over the past two weeks (10 items, 5-point Likert scale, with scores expressed on a scale of 0–100). We also used the Perceived Stress Scale (PSS, 14 items, 5-point Likert scale) to assess past-month feelings of being upset, nervous, angered, lacking control, or being unable to cope. While developed in Western contexts (Cohen et al., 1983), the Arabic-language PSS was validated in Jordan (Almadi et al., 2012). Finally, we implemented the Children's Revised Impact of Event Scale (CRIES, 8 items, 5-point Likert scale) to assess posttraumatic stress reactions. CRIES has good psychometric properties in war-affected Arab populations (Veronese and Pepe, 2013; Punamäki

et al., 2015). The War Child Foundation recommends CRIES-8 as a screening tool that is predictive of posttraumatic stress reactions (using a threshold of intrusion and avoidance symptoms ≥17 points for meeting diagnostic criteria of PTSD). Many studies nonetheless rely on dimensional CRIES scores in analytical models, given that this threshold is predictive rather than diagnostic of PTSD (Tol et al., 2011a,b; Tol et al., 2013; Panter-Brick et al., 2015).

2.1.3. Stress biomarkers

In order to appraise which measures would be most appropriate for impact evaluation in humanitarian settings, we began the study with a range of relatively non-invasive stress biomarkers: these included blood pressure, cell-mediated immune function from dried blood spots, DNA samples from cheek swabs, and cortisol production from saliva and hair samples (Sancilio et al., 2016). It soon became clear that saliva sampling was the most burdensome measure for participants – for whom 'spitting' proved socially embarrassing, as well as for researchers, given that collecting multiple samples to account for diurnal variation was relatively time-consuming and shipping samples was expensive. By contrast, study participants appreciated our offer of a free professional haircut and did not find hair sampling invasive, and the fieldworkers found collecting and processing hair to be simpler as well. We employed local hairdressers to cut ~100 strands of hair, as close as possible to the scalp from the vertex posterior, and give participants a professional haircut: this rewarded them for their time and ensured that sampling would be minimally visible. Hair samples were cut at each of the three time-points.

2.1.4. Laboratory analysis

Hair samples were sent to the Drug Safety Laboratory (DSLab) of the Robarts Research Institute at the University of Western Ontario, which has been conducting hair cortisol analyses for over 10 years (e.g. Van Uum et al., 2008; Thomson et al., 2010; Pereg et al., 2013), including HCC analyses in conflict-affected populations (Etwel et al., 2014). We measured cortisol concentrations of hair (0–2 cm at baseline, 0–1 cm at T2, 0–1 cm at T3). Hair was black or brown, and undyed. Hair samples were cut into segments, weighed, and washed twice for 3 min with 3 mL of isopropanol before being dried for a minimum of 5 h. Dried samples were then minced and extracted in 2 mL of methanol at 56 ° Celsius in an incubator shaker for 16 h. Methanol (containing cortisol extract) was removed to a clean tube and evaporated under heat and nitrogen gas until dry. Dried samples were reconstituted with 0.25 mL of phosphate buffered saline (pH = 8) before undergoing ELISA testing to quantify cortisol levels using a modified commercially available salivary cortisol test kit. The intra- and inter-day coefficients of variation for the cortisol immune assay were 3.6% and 8.6%, respectively. ELISA testing uses high and low cortisol controls on each plate for the generation of a plate-specific standard curve. Subsequently, each sample was individually compared with its plate-specific standard curve. Samples from different time-points were analyzed on separate plates.

2.1.5. Statistical analysis

Cortisol data were log-transformed to normalize the distribution. In line with other studies (e.g. Skoluda et al., 2012), we excluded data points more than +2SD from the mean: namely, 5 outliers at T1, 15 at T2, and 26 at T3 (pre-log HCC exceeding 90 pg/mg). This resulted in the removal of only six participants, as most had at least one additional measurement at another time-point which fell within the normal range. Our sample included 150 participants with cortisol data at all time-points, 413 with cortisol data for at least two time-points, and 727 with cortisol data for at least one time-point. We used both growth mixture and growth curve models to test our hypotheses; unlike traditional statistical models that involve listwise deletion for missing data, these models are robust to partially missing and unequally spaced data (Curran et al., 2010; Ram and Grimm, 2009).

First, we examined sociodemographics and trends in the variables over time. To better understand how trauma exposure predicts cortisol regulation over time, we split the sample into those who had experienced less than (< 4) and more than average trauma (≥4 events), and ran Pearson correlations between cortisol at each time-point. We then used the full sample to study longitudinal cortisol trajectories with latent growth mixture modeling in MPlus v7.3. This technique captured heterogeneity in cortisol over time in k number of groups (or classes), each with a distinct trajectory, enabling us to test whether there were multiple trajectories of cortisol production. To determine the optimal number of classes, we added classes one at a time to examine whether model fit improved with each additional class; the four-class model was not significant, so we did not continue further (Jung and Wickrama, 2008). The slopes and intercepts were allowed to vary freely across classes, but held constant within groups.

To establish the underlying pattern of cortisol trajectories in our data, we used Ram and Grimm's (2009) well-established technique for selection of the optimal number of latent classes within a sample over time. First, we examined the Akaike Information Criteria (AIC) and sample-size adjusted Bayesian Information Criteria (SSA-BIC). A lower value indicates better model fit. We then examined the Vuong-Lo-Mendell-Rubin likelihood ratio test and Adjusted Lo-Mendell-Rubin tests, to determine whether each model performed better than the model with k-1 classes. The three-class model was significant for both, indicating that a three-trajectory solution fits the data better than a two-trajectory solution. Participants were assigned to the latent class that best fitted their trajectory. To assess predictors of class membership, we conducted a multinomial logistic regression in SPSS v.24, with the middle category (Medium Secretion) as the reference group. We included insecurity, perceived stress, posttraumatic stress symptoms, and gender at T1 as predictors. We also conducted sensitivity analyses with resilience scores and other potentially important variables, such as age, site, wealth, and trauma exposure; adding these variables did not impact or change regression results (data available upon request).

Next, we used growth curve modeling to examine whether participating in the intervention predicted changes in cortisol production over time. Growth curve modeling is a powerful predictive statistical technique to assess both within- and between-person variation (Hruschka et al., 2005; Van Ryzin et al., 2009); in this dataset, we have repeated measurements (level one) nested within participants (level two). First, we ran models for the overall cohort in order to test intervention impacts. Then we added interaction terms to test whether the intervention impact differed by HCC trajectory, as well as by participant characteristics such as levels of insecurity, stress, posttraumatic stress, gender, and trauma exposure.

We then tested patterns of stress responsivity for adolescents who experienced more than average trauma (≥4 events), with the expectation that those who had developed PTSD reactions were more vigilant to their environments than those who did not, despite similar levels of exposure to trauma. We ran the growth curve model in this restricted sample, and tested the interaction between participating in the intervention and PTSD group. We repeated these models with a three-way interaction with resilience added (as an interaction term, intervention*PTSD*resilience), as we hypothesized that individual, relational, and contextual protective factors may influence whether and how the PTSD group responded to the intervention.

In all growth models, we included four time-invariant covariates (baseline: gender, age, site, and household wealth), coded trial participation as time-varying, and used maximum likelihood estimation to handle missing data. At T1 (baseline), no participants had taken part in the intervention (all were given a score of 0). At T2 and T3, those in the treatment group were given a score of 1, and those in the control group a score of 0. We used a first-order autoregressive covariance matrix.

3. Results

We achieved a gender-balanced sample, half of whom were Syrian

Table 1
Characteristics of study participants, at three time-points.

	Baseline, T1 (n = 611)	11 weeks, T2 (n = 439)	11 months, T3 (n = 236)
Age (years)	14.52 (1.70)	14.38 (1.71)	14.17 (1.75)
Male (%)	46.5	51.1	56.2
Syrian refugee (%)	57.6	56.9	61.0
Study site (%), Irbid	28.2	26.9	17.8
Mafraq	23.4	19.6	28.4
Jarash	34.4	35.5	36.4
Zarqa	14.1	18.0	17.4
Trial group (% intervention)	58.9	56.3	54.7
Household wealth (N items)	7.76 (2.92)	7.82 (2.89)	7.49 (2.99)
Trauma exposure (N events)	4.03 (3.73)	3.99 (3.72)	4.29 (3.63)
PTSD (%)	44.7	44.1	47.1
CRIES	13.56 (12.62)	13.08 (12.79)	14.00 (12.52)
Perceived stress	27.87 (6.43)	25.26 (6.55)	23.04 (9.48)
Human insecurity	63.81 (21.29)	59.33 (22.50)	57.95 (20.43)
Hair cortisol (pg/mg, non-transformed)	9.52 (9.98)	10.01 (14.46)	16.28 (18.74)
Hair cortisol (log pg/mg)	0.82 (0.37)	0.65 (0.59)	0.92 (0.55)

Unless otherwise stated, values are mean (*SD*). Values for age, gender, nationality, study site, trial group, household wealth, trauma exposure, PTSD, and CRIES scores are from T1; values presented at T2 and T3 reflect change from attrition. Values for perceived stress, insecurity, and hair cortisol (collected at T1, T2, and T3) are shown for each time-point, reflecting change over time. For group differences, please see text and Table 4.

refugees, totalling 727 participants in four urban centers: Irbid (n = 183), Mafraq (n = 165), Jarash (n = 265), and Zarqa (n = 114). These participants had cortisol data, at a minimum, at one time-point. At baseline, physiological and psychological data were available for 611 participants (57.6% Syrian, 46.5% male, mean age = 14.52 years, SD = 1.70), 439 participants at T2, and 236 participants at T3 (Table 1). Reasons for attrition were that youth were unreachable or unavailable, due to illness or school/work (Panter-Brick et al., 2017a).

3.1. Descriptive data on trauma exposures and cortisol

Syrian refugees were exposed to significant trauma: they averaged 6.25 lifetime trauma exposures (SD = 3.25) as compared to 1.06 trauma (SD = 1.68) for Jordanians ($p < 0.001$). The most common traumatic experiences to which the Syrian refugees were exposed were: witnessing bombardment or explosions (80.6%), having their home forcibly searched by police or a militia (71.0%), witnessing the demolition of their home by police or a militia (55.0%), living in a refugee camp (53.1%), and seeing a wounded or dead body (52.6%). By contrast, non-refugees reported a lack of medical care when severely ill (16.6%), seeing someone beaten, shot, or killed (15.3%), having a bad accident or fall (12.8%), painful or frightening medical treatment (9.7%), and being severely beaten (8.1%). Two-thirds of adolescent refugees (65.2%) had symptoms of intrusion and avoidance consistent with PTSD reactions (≥ 17 CRIES points), as compared to 18.8% of Jordanians.

At baseline, there was no significant relationship between HCC and trauma exposure (as measured by number of lifetime trauma events, $p > 0.05$). However, participants who met criteria for PTSD had higher baseline HCC (M = 0.86, SD = 0.34) than those who did not (M = 0.79, SD = 0.39; $t(608) = 2.31$ p = 0.02). While Syrian refugees had higher levels of post-traumatic stress symptoms, perceived stress, and insecurity ($p < 0.001$) relative to Jordanian non-refugees, their HCC were similar to those of Jordanians ($p > 0.05$) at all three time-points. Girls had higher HCC than boys ($p < 0.001$) at all time-points. We found no gender differences in likely PTSD (baseline CRIES ≥17 points: 45.5% for girls, 43.8% for boys, p = 0.67), except at T3, where more girls than boys met predictive criteria [χ^2 (1, N = 186) = 4.90, p = 0.03].

We tabulated Pearson correlations of cortisol levels at all three time-points for the cohort stratified by average sample trauma exposure (< 4 trauma events, ≥4 trauma events; Table 2). Adolescents with lower trauma exposures (n = 364, 20.3% Syrian) had cortisol levels that were, as could be expected, correlated over time (rs = 0.25 to 0.42, $p < 0.05$). By contrast, adolescents exposed to 4 or more lifetime traumas (n = 363, 91.7% Syrian) exhibited a pattern of cortisol dysregulation, where hair cortisol production was unrelated to itself over time (rs = 0.13 to 0.19, $p > 0.05$). In terms of the sample with or without PTSD, we observed the following pattern: For adolescents *without* PTSD, hair cortisol levels were correlated at all three time-points (rs range from 0.21 to 0.34, $p < 0.05$), while for adolescents *with* PTSD, cortisol levels were correlated from T1 to T2 (r = 0.23, $p < 0.05$) but unrelated from T2 to T3 (r = 0.17, $p > 0.05$) or from T1 to T3 (r = 0.16, $p > 0.05$).

Table 2
Correlations for cortisol over time, for the sample stratified by lifetime trauma exposure.

	T1 Cortisol	T2 Cortisol
Low trauma exposure		
T2 Cortisol	0.42** (n = 173)	
T3 Cortisol	0.29* (n = 74)	0.25* (n = 88)
High trauma exposure		
T2 Cortisol	0.13 (n = 180)	
T3 Cortisol	0.19 (n = 97)	0.13 (n = 105)

Pearson correlations for hair cortisol content (log values). Low trauma exposure is < 4 trauma events, high trauma exposure is ≥4 trauma events.
* $p < 0.05$.
** $p < 0.001$.

3.2. Cortisol trajectories: impacts of insecurity, stress, and posttraumatic stress

We observed three HCC trajectories, as indicated by fit indices for growth mixture modeling (Table 3, Supplemental Table A). As seen in Fig. 1, the first class (Hypersecretion, n = 70) had a baseline log cortisol of 1.34 pg/mg and decreased by 0.04 each month during the study period. The second class (Medium Secretion, n = 636) had a baseline log cortisol of 0.77 pg/mg and increased by 0.01 each month. The third class (Hyposecretion, n = 21) had a baseline log cortisol of −1.47 pg/mg and increased by 0.07 per month. Essentially, adolescents in the Hypersecretion class (comprising 9.6% of the sample) started high and experienced shallow decreases in cortisol, those in the Medium Secretion class (87.5% of the sample) started at a mid-range and increased slightly, and those in the Hyposecretion class (2.9% of the sample) started very low and increased rapidly in cortisol. Analysis of the distribution of trajectories across the ELISA plates excluded distribution across plates as a potential confounder ($p > 0.05$). Overall, log cortisol went up over the course of the study (from M = 0.82 at T1 to 0.92 at T3, Table 1): thus, while there were individual trajectories of cortisol production, the trend for the sample as a whole was an increase in cortisol over time.

Insecurity and post-traumatic stress, but not psychosocial stress, predicted HCC trajectories (Table 4). Adolescents who reported higher

Table 3
Model fit for latent basis mixture models of hair cortisol content.

	AIC	SSA-BIC	Entropy	LMR	VLMR
2 class	1691.90	1704.70	0.92	29.98**	0.28**
3 class	**1669.25**	**1686.32**	**0.78**	**27.27****	**3.32****
4 class	1661.90	1683.23	0.52	12.71	11.69

Note: Significant LMR and VLMR scores suggest better model fit than a k-1 class model. Based on fit indices and theory, the 3-class model was chosen. LMR = Lo-Mendell-Rubin likelihood ratio test, VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test.
** $p < 0.001$.

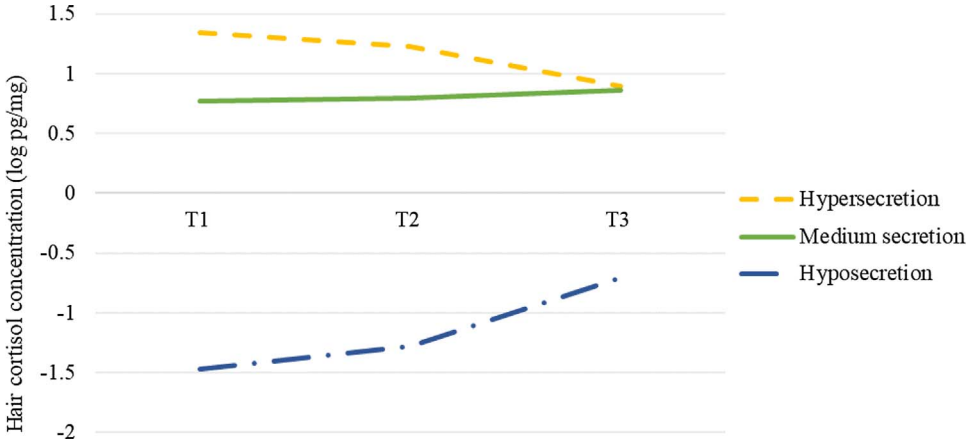

Fig. 1. Trajectories of hair cortisol concentration over time.
The three groups differ at T1 and T2 (independent samples *t*-tests, $p < 0.05$). Neither the hyposecretion nor the hypersecretion groups differ from the medium secretion group at T3 ($p > 0.05$). Insecurity and gender predict a pattern of hypersecretion and post-traumatic stress symptoms predict a pattern of medium secretion rather than hyposecretion. T1 is baseline, T2 is after 2.8 months, and T3 is after 11.1 months. These data include all study participants.

Table 4
Multinomial logistic regression, predicting cortisol trajectory membership from gender, baseline trauma, perceived stress, and insecurity.

	B	*SE*	e^B	Wald Z	*p*	95% CI
Hyposecretion						
Gender	−0.08	0.46	0.92	0.03	0.86	0.38, 2.27
CRIES	−0.07	0.03	0.93	7.68	0.01	0.89, 0.98
Perceived stress	0.03	0.04	1.03	0.47	0.49	0.95, 1.11
Human insecurity	0.00	0.01	1.00	0.09	0.76	0.98, 1.02
Hypersecretion						
Gender	−1.57	0.31	0.21	24.96	< 0.001	0.11, 0.39
CRIES	0.00	0.01	1.00	0.00	0.98	0.98, 1.02
Perceived stress	−0.01	0.02	0.99	0.36	0.55	0.95, 1.03
Human insecurity	0.02	0.01	1.02	6.61	0.01	1.00, 1.03

Note: Reference class is the Medium Secretion class. Reference group for gender is female.

insecurity were more likely to be part of the Hypersecretion trajectory ($B = 0.02$, SE = 0.01, 95% CI: 1.00, 1.03, $p = 0.01$). With each percentage point increase in their feelings of fear and insecurity (on a scale of 0–100%), youth were 0.02 times more likely to show hyper cortisol secretion. Moreover, holding other variables constant, girls were likely to be in the Hypersecretion category than boys ($B = -1.57$, SE = 0.31, 95% CI: 0.11, 0.39, $p < 0.001$). Adolescents reporting more post-traumatic stress reactions were less likely to be part of the Hyposecretion trajectory ($B = -0.07$, SE = 0.03, 95% CI: 0.89, 0.98, $p = 0.01$). For every additional point on the CRIES, adolescents were 0.07 times less likely to be categorised in the Hyposecretion class relative to the Medium Secretion class. This suggests that insecurity and post-traumatic stress symptoms predict different patterns of cortisol production over time.

3.3. Impacts of the intervention

We found that HCC of adolescents engaged in the intervention went up at a slower rate ($B = -0.11$, $SE = 0.04$, 95% CI: −0.19, −0.03, $p = 0.01$), relative to the control group, in growth curve models adjusting for gender, age, site, and wealth (Supplemental Table B). Girls had higher HCC at intercept than boys, but their change in HCC over time (slope) was the same. Similarly, older participants had higher HCC, but their HCC slope was the same as younger participants. The intervention attenuated cortisol production by a third (Fig. 2; Supplemental Table B).

The benefits of the intervention (in terms of lowering HCC) were similar for all participants, whether boys or girls, Syrian or Jordanians with high or low trauma exposures, or adolescents with different levels of insecurity, stress, or posttraumatic reactions ($p > 0.05$, model tables available by request). However, there were notable differences by HCC

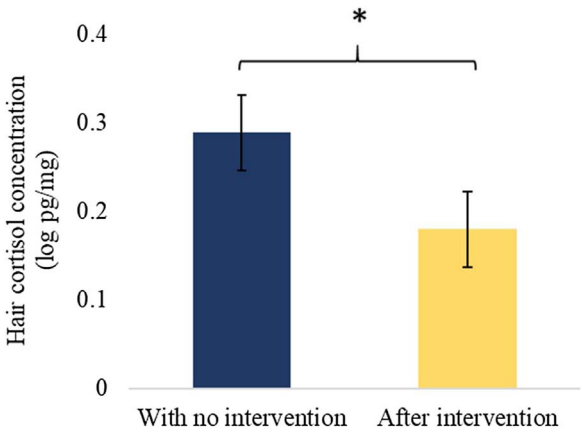

Fig. 2. Impacts of the psychosocial intervention on hair cortisol concentration. Across time, the intervention significantly reduced hair cortisol concentration for those who were in the treatment group, relative to wait-listed controls (a 37.8% decrease). The figure shows within-subjects change over time when taking part in the intervention. Growth curve model controls for gender, age, site, and household wealth.
*$p < 0.05$, error bars are ± 1SE.

trajectory: the intervention raised rather than lowered HCC for the Hyposecretion class (Fig. 3). When Hyposecretion adolescents engaged in the intervention, their cortisol levels increased by 59.7% ($B = 0.69$, $SE = 0.24$, 95% CI: 0.22, 1.16, $p = 0.004$) relative to the control group wait-listed for the intervention. We found no difference in intervention impacts on cortisol production between the Hypersecretion and Medium Secretion classes ($B = 0.04$, $SE = 0.13$, 95% CI: −0.21, 0.29, $p > 0.05$), where participating in the intervention decreased cortisol by 15.2% for the Hypersecretion group, and 43.2% for the Medium Secretion group.

We then examined whether HCC trajectories differed for participants with and without posttraumatic stress reactions akin to PTSD, who might be more or less vigilant to their environments, restricting the sample to those with high-trauma exposure (≥4 events, $n = 363$). The interaction between PTSD and participation in the intervention was non-significant ($p > 0.05$). Individual resilience scores did not moderate this relationship ($p > 0.05$).

4. Discussion

In this study, we obtained unique psychological and hair cortisol data for adolescents directly and indirectly affected by the violence of war and forced displacement. We assessed a large, gender-balanced, representative sample of vulnerable youth, through engaging with refugee and host communities living side-by-side in urban centers in

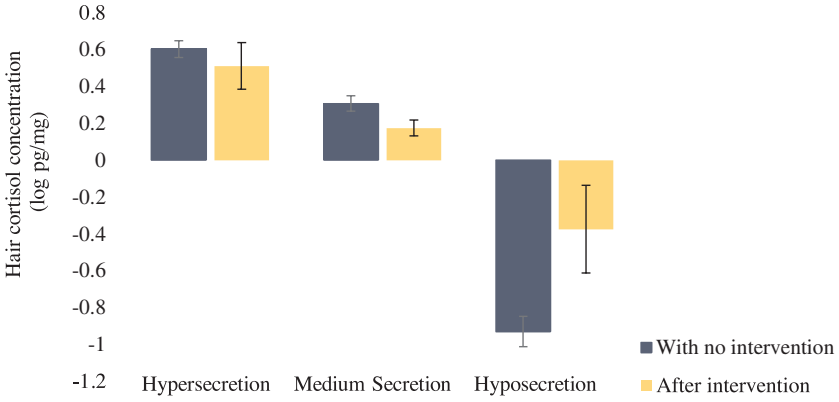

Fig. 3. Impacts of the psychosocial intervention on hair cortisol concentration (HCC). The interaction (intervention*cortisol trajectory) was significant ($p < 0.05$). Across time, growth curve models showed that the intervention reduced HCC for adolescents with a hypersecretion and medium secretion trajectory (by 15.2% and 43.2%, respectively), but increased HCC for those with a hyposecretion trajectory (by 59.7%). Model controls for gender, age, site, and household wealth.

northern Jordan, close to the border with Syria. To our knowledge, ours is the first study both to establish trajectories of cortisol production in war-affected adolescents, and to prospectively assess the impact of a brief and scalable humanitarian intervention targeting psychosocial wellbeing. By integrating measures of HCC over time, we identified three trajectories of cortisol production: Hypersecretion, Medium Secretion, and Hyposecretion. We found that the stress-attunement intervention (Mercy Corps, 2014, 2016) was effective in regularizing cortisol production over time: as indexed by hair cortisol concentrations, it decreased levels of chronic stress by a third.

We highlight three main findings in this study. First, experiencing fear or insecurity was predictive of a trajectory of increased cortisol production (Hypersecretion in Fig. 1 and Table 3). This is consonant with previous research on the salience of current stressors (Stalder et al., 2017). Over the long-term, heightened cortisol production can have negative effects on health, which include depression, memory and learning deficits, overweight, high blood glucose, and high blood pressure (Tirabassi et al., 2014; Wosu et al., 2013). Considering that half our sample (54.9%) reported high insecurity levels at baseline, the finding that experiences of fear and insecurity were associated with chronic cortisol hypersecretion is an important one, worthy of further investigation in situations of war and forced displacement.

Second, we observed that the beneficial impacts of the *Advancing Adolescents* intervention – previously established for mental health and psychosocial outcomes (Panter-Brick et al., 2017a) – were mirrored in physiological response. This intervention altered HPA activity, as shown by models that controlled for gender, age, site, and household wealth. For the overall cohort, we found that the intervention led to a 37.8% decrease in cortisol production over time (Fig. 2). In the hypersecretion and medium secretion classes, the intervention led to reductions in cortisol (of 15.2% and 43.2%, respectively), but in the Hyposecretion class – which had very low baseline levels of HCC – it led to a 59.7% increase in cortisol (Fig. 3). This suggests that effective psychosocial interventions may lead to a normalization of cortisol levels in either direction (up- or down-regulation). This is likely beneficial, since chronic hyposecretion also has negative effects on mental and physical health, being associated with impaired stress responses (Johannsson et al., 2015), bodily disorders (Heim et al., 2000), and aggressive behavior (White et al., 2017).

Third, we found that, at the individual level, high-trauma youth exhibited hair cortisol concentrations that were likely dysregulated, being unrelated at each time-point (as shown by weak individual-level correlation coefficients, Table 2). These findings may be specific to population groups experiencing many frightening and distressing experiences: in our sample, 91.7% in the high-trauma exposure group were forcibly displaced Syrian refugees ($n = 333$). As global studies have shown, experiencing this number of adverse childhood experiences predicts both the occurrence and the onset of psychopathology in later adulthood (Kessler et al., 2010). We then looked for non-linear patterns of stress responsivity, predicted by the adaptive calibration model (Del Giudice et al., 2012), but did not find strong evidence that either gender or PTSD status impacted physiological responses to the intervention. We are currently incorporating genetic data, assayed from DNA extracted from cheek swabs collected from study participants, to investigate the genetic component of stress responsivity (Clukay et al., 2018).

Our analyses to-date show that the 8-week stress-attunement intervention had likely beneficial physiological impacts for the cohort as a whole: with respect to cortisol, the intervention was similarly effective for all participants, whether male or female, refugee or non-refugee, irrespective of insecurity, stress, or posttraumatic stress reactions. This has important implications. For example, experimental trials of unconditional cash transfers in Kenya have interpreted a reduction in psychosocial stress and cortisol levels as gaining 'peace of mind' (Haushofer et al., 2017). They also show that different types of intervention have likely differential impacts. However, these trials included the collection of just two saliva samples (one pre- and one post-intervention) to assess wellbeing. Further research will need to clarify the extent to which beneficial physiological impacts are sustained, and the extent to which they improve social, developmental, or cognitive function.

We noted that participation in the programme could lead to either increased or attenuated cortisol production, which may explain patterns of cortisol dysregulation in youth experiencing 4 or more traumatic events. To-date, there are conflicting findings as to whether posttraumatic stress symptoms and traumatization are linked to hyper- or hypocortisolism (Steudte et al., 2011, 2013; Fischer et al., 2017). This may account for the non-uniform results observed in our study at high-trauma exposures: where trauma caused hypocortisolism, we may have detected an upward normalization, and where trauma increased cortisol responses, the intervention may have stabilized, decreased, and/or normalized cortisol production. In settings of conflict and extensive trauma, where memories of trauma are malleable and present heterogeneous associations with posttraumatic distress (Panter-Brick et al., 2015), more research is needed to study both the impacts of psychosocial interventions and the etiology of hyper- and hypocortisolism.

Unfortunately, there is limited research establishing what HCC levels and/or trajectories might be expected in this age-group. A study by Dettenborn et al. (2012) suggested that children tend to have higher cortisol levels than young adults, while Noppe et al. (2014) showed a gradual increase in hair cortisol with age, including higher reference intervals for the age 10–14 group than for younger age groups. White et al. (2017) also demonstrated a gradual increase of HCC with age in their control population, while reporting a relative reduction in maltreated children and adolescents (3–16 year old) in Germany. A slight increase of hair cortisol over time (.10 log pg/mg over the 11 month-period) is therefore consistent with the literature. In this study, we cannot infer age-related HPA responses from observed cohort-level HCC changes, given the short time-frame and the multiple roles this

hormone plays in regulating stress, metabolism, and immune responses.

This study has two main limitations. First, we relied on hair cortisol levels, which provide a measure of cortisol hormone production averaged over time. HCC incorporate circadian fluctuations in a monthly average, but unlike serum or saliva, does not permit analysis of dynamic responses. At the start of our study, we implemented both saliva and hair cortisol sample collection, but found that collecting multiple saliva samples was not logistically feasible in this humanitarian aid context. By contrast, hair cortisol sampling proved a workable choice, particularly as we offered participants a complimentary haircut at the time of measurement. While we did not capture other factors that may affect hair cortisol, including strenuous exercise and frequency of hair washing, we did not find a difference in HCC between those participants who were and who were not engaged in physical activity, and we avoided all sampling during the fasting month of Ramadan, which considerably alters social and physical activity. Second, we collected cohort data at only three points, thus capturing a limited period of time change, and saw substantial cohort attrition. In conflict and refugee settings, extensive loss-to-follow-up arises from difficulties in tracking participants, yet in robustly-designed surveys, losses of even two-thirds of a refugee cohort has been shown to entail little retention bias with respect to mental health (Panter-Brick et al., 2013). Methodologically, we were able to use growth models to capture between- and within-individual differences in cortisol production, with models that are robust to missing values and uneven data points, in line with best practices for our study goals (Hruschka et al., 2005; Van Ryzin et al., 2009).

5. Conclusion

Temporal examinations of endocrine changes as a biological signature of stress or trauma in war-affected civilian populations are seldom undertaken, given the demands of a longitudinal research design to follow large enough cohorts over time. A major strength of our study lies in its robust prospective design (a randomized control trial, with surveys at three time-points). This allowed us to observe the physiological impacts of a brief psychosocial intervention, to assess whether differential impacts were observed for distinct classes of cortisol production over time, and to examine whether some adolescents were more sensitive to improved environments. We conducted the impact evaluation with a gender-balanced, community-based sample of Syrian refugees and Jordanian hosts who were differentially impacted by the trauma of war and the insecurity of forced displacement (Panter-Brick et al., 2017a,b).

Our work exemplifies the utility of biomarkers for tracking changes in physiological stress in response to past trauma, current insecurity, and structured psychosocial interventions. In contexts of war and forced displacement, this has value for understanding whether improving day-to-day environments, through the alleviation of current psychosocial stressors, can have beneficial physiological consequences and protect adolescent health and development. Indeed, we see that effective interventions can improve not just self-reports of insecurity, stress, and mental health difficulties (Panter-Brick et al., 2017a,b), but can also change and regulate young people's physiology. This study thus contributes to a body of work seeking to better understand the trajectories of neuroendocrine response in adverse environments, as well as patterns of stress responsivity to short-term ecological improvement.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.psyneuen.2017.12.012.

References

Almadi, T., Cathers, I., Mansour, A.M.H., Chow, C.M., 2012. An Arabic version of the perceived stress scale: translation and validation study. Int. J. Nurs. Stud. 49, 84–89.
Bakermans-Kranenburg, M.J., van IJzendoorn, M.H., 2015. The hidden efficacy of interventions: gene × environment experiments from a differential susceptibility perspective. Annu. Rev. Psychol. 66, 381–409.
Boyce, W.T., Ellis, B.J., 2005. Biological sensitivity to context: i. An evolutionary–developmental theory of the origins and functions of stress reactivity. Dev. Psychopathol. 17, 271–301.
Clukay, C., Dajani, R., Hamadmad, D., Abudayyeh, G., Panter-Brick, C., Mulligan, C., 2018. Genetics of risk and trauma exposure in Syrian refugee youth. Meeting of the American Association of Physical Anthropologists (April).
Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385–396.
Curran, P.J., Obeidat, K., Losardo, D., 2010. Twelve frequently asked questions about growth curve modeling. J. Cogn. Dev. 11, 121–136.
Del Giudice, M., Ellis, B.J., Shirtcliff, E.A., 2011. The adaptive calibration model of stress responsivity. Neurosci. Biobehav. Rev. 35, 1562–1592.
Del Giudice, M., Hinnant, J.B., Ellis, B.J., El-Sheikh, M., 2012. Adaptive patterns of stress responsivity: a preliminary investigation. Dev. Psychol. 48, 775–790.
Dettenborn, L., Tietze, A., Kirschbaum, C., Stalder, T., 2012. The assessment of cortisol in human hair: associations with sociodemographic variables and potential confounders. Stress 15, 578–588.
Etwel, F., Russell, E., Rieder, M.J., Van Uum, S.H., Koren, G., 2014. Hair cortisol as a biomarker of stress in the 2011 Libyan war. Clin. Invest. Med. 37, 403–408.
Fernald, L.C., Gunnar, M., 2009. Poverty-alleviation program participation and salivary cortisol in vey low-income children. Soc. Sci. Med. 68, 2180–2189.
Fischer, S., Duncko, R., Hatch, S.L., Papadopoulos, A., Goodwin, L., Frissa, S., Hotopf, M., Cleare, A.J., 2017. Sociodemographic, lifestyle, and psychosocial determinants of hair cortisol in a South London community sample. Psychoneuroendocrinology 76, 144–153.
Gola, H., Engler, H., Maggie, S., Adenauer, H., Riether, C., Kolassa, S., Elbert, T., Kolassa, I.T., 2012. Victims of rape show increased cortisol responses to trauma reminders: a study in individuals with war- and torture-related PTSD. Psychoneuroendocrinology 37, 213–220.
Hadfield, K., Ostrowski, A., Ungar, M., 2017. What can we expect of the mental health and well-being of Syrian refugee children and adolescents in Canada? Can. Psychol. 58, 194–201.
Hamayel, L., Ghandour, R., Abu Rmeileh, N., Giacaman, R., 2014. Assessment of the Psychosocial Health Status of Adolescents 12–18 Years Old in the Occupied Palestinian Territory: A Cross Sectional Baseline Survey. Birzeit University, Institute of Community and Public Health, Palestine.
Haushofer, J., Shapiro, J., 2016. The short-term impact of unconditional cash transfers to the poor: experimental evidence from Kenya. Q. J. Econ. 131 (4), 1973–2042.
Haushofer, J., Chemin, M., Jang, C., Abraham, J., 2017. Peace of mind: health insurance reduces stress and cortisol levels – evidence from a randomized experiment in Kenya. JEL February. https://www.princeton.edu/haushofer/publications/Haushofer_Chemin_Jang_Abraham_Insurance_2017.02.10_jh.pdf.
Heim, C., Ehlert, U., Hellhammer, D.H., 2000. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 25, 1–35.
Hruschka, D.J., Kohrt, B.A., Worthman, C.M., 2005. Estimating between- and within-individual variation in cortisol levels using multilevel models. Psychoneuroendocrinology 30, 698–714.
Johannsson, G., Falorni, A., Skrtic, S., Lennernäs, H., Quinkler, M., Monson, J.P., Stewart, P.M., 2015. Adrenal insufficiency: review of clinical outcomes with current glucocorticoid replacement therapy. Clin. Endocrinol. 82, 2–11.
Jung, T., Wickrama, K.A.S., 2008. An introduction to latent class growth analysis and growth mixture modeling. Soc. Pers. Psychol. Compass 2, 302–317.
Kessler, R.C., McLaughlin, K.A., Green, J.G., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Aguilar-Gaxiola, S., Alhamzawi, A.O., Alonso, J., Angermeyer, M., Benjet, C., Bromet, E., Chatterji, S., de Girolamo, G., Demyttenaere, K., Fayyad, J., Florescu, S.,

Gal, G., Gureje, O., Haro, J.M., Hu, C.Y., Karam, E.G., Kawakami, N., Lee, S., Lépine, J.P., Ormel, J., Posada-Villa, J., Sagar, R., Tsang, A., Ustün, T.B., Vassilev, S., Viana, M.C., Williams, D.R., 2010. Childhood adversities and adult psychopathology in the WHO world mental health surveys. Br. J. Psychol. 197, 378–385.

Li, X., Huang, W.X., Lu, J.M., Yang, G., Ma, F.L., Lan, Y.T., Meng, J.H., Dou, J.T., 2012. Experimental study on neuroendocrinological and immunological characteristics of the military-trained artillerymen. Chin. Med. J. 125, 1292–1296.

Luo, H., Liu, X., Ma, X., Guo, W., Qiu, C., Wang, Y., Wang, Q., Zhang, X., Zhang, W., Hannum, G., Zhang, K., Liu, X., Li, T., 2012. Hair cortisol level as a biomarker for altered hypothalamic-pituary-adrenal activity in female adolescents with postraumatic stress disorder after the 2008 Wenchuan earthquake. Biol. Psychiatry 72, 65–69.

Macphail, J., Niconchuk, M., El-wer, N., 2017. Conflict, the brain, and community: a neurobiology-informed approach to resilience and community development. In: Phillips, R., Kenny, S., McGrath, B. (Eds.), The Routledge Handbook of Community Development, Human Rights and Resilience, London, United Kingdom.

Masoudzadeh, A., Modanloo, K.M., Ajami, A., Azizi, A., 2012. Evaluation of cortisol level and cell-mediated immunity response changes in individuals with post-traumatic stress disorder as a consequence of war. Med. Glas. 9, 218–222.

McEwen, B.S., 2012. Brain on stress: how the social environment gets under the skin. Proc. Natl. Acad. Sci. U. S. A. 109, 17180–17181.

Corps, Mercy, 2014. Advancing Adolescents: Getting Syrian Refugee and Host-community Adolescents Back on Track. Portland, Oregon.

Mercy Corps, 2016. NUBADER Advancing the Next Generation: Final Evaluation Report. . https://www.mercycorps.org/ (Accessed 01.07.17).

Mewes, R., Reich, H., Skoluda, N., Seele, F., Nater, U.M., 2017. Elevated hair cortisol concentrations in recently fled asylum seekers in comparison to permanently settled immigrants and non-immigrants. Transl. Psychol. 7, e1051.

Miller, K.E., Rasmussen, A., 2010. War exposure, daily stressors, and mental health in conflict and post-conflict settings: bridging the divide between trauma-focused and psychosocial frameworks. Soc. Sci. Med. 70, 7–16.

Miller, G.E., Chen, E., Zhou, E.S., 2007. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol. Bull. 133, 25–45.

Noppe, G., Van Rossum, E.F., Koper, J.W., Manenschijn, L., Bruining, G.J., De Rijke, Y.B., van den Akker, E.L., 2014. Validation and reference ranges of hair cortisol measurement in healthy children. Horm. Res. Paediatr. 82, 97–102.

Panter-Brick, C., Eggerman, M., Gonzalez, V., Safdar, S., 2009. Violence, suffering, and mental health in Afghanistan: a school-based survey. Lancet 374, 807–816.

Panter-Brick, C., Grimon, M., Eggerman, M., 2013. Caregiver-child mental health: a prospective study in conflict and refugee settings. J. Child Psychol. Psychiatry 55, 313–327.

Panter-Brick, C., Grimon, M.-P., Kalin, M., Eggerman, M., 2015. Trauma memories, mental health, and resilience: a prospective study of Afghan youth. J. Child Psychol. Psychiatry 56, 814–825.

Panter-Brick, C., Dajani, R., Eggerman, M., Hermosilla, S., Sancilio, A., Ager, A., 2017a. Insecurity, distress and mental health: experimental and randomized controlled trials of a psychosocial intervention for youth affected by the Syrian crisis. J. Child Psychol. Psychiatry.

Panter-Brick, C., Hadfield, K., Dajani, R., Eggerman, M., Ager, A., Ungar, M., 2017b. Resilience in context: a brief and culturally grounded measure for Syrian refugee and Jordanian host-community adolescents. Child Dev.

Pereg, D., Chan, J., Russell, E., Berlin, T., Mosseri, M., Seabrook, J.A., Koren, G. Van Uum, 2013. Cortisol and testosterone in hair as biological markers of systolic heart failure. Psychoneuroendocrinology 38, 2875–2882.

Pluess, M., Belsky, J., 2013. Vantage sensitivity: individual differences in response to positive experiences. Psychol. Bull. 139 (4), 901–916.

Punamäki, R.L., Palosaari, E., Diab, M., Peltonen, K., Qouta, S.R., 2015. Trajectories of posttraumatic stress symptoms (PTSS) after major war among Palestinian children: trauma, family-and child-related predictors. J. Affect. Disord. 172, 133–140.

Ram, N., Grimm, K.J., 2009. Methods and measures: growth mixture modeling: a method for identifying differences in longitudinal change among unobserved groups. Int. J. Behav. Dev. 33, 565–576.

Russell, E., Koren, G., Rieder, M., van Uum, S., 2012. Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. Psychoneuroendocrinology 37, 589–601.

Russell, J.D., Neill, E.L., Carrion, V.G., Weems, C.F., 2017. The network structure of posttraumatic stress symptoms in children and adolescents exposed to disasters. J. Am. Acad. Child Adolesc. Psychiatry 56, 669–677 e665.

Sancilio, A., Dajani, R., Eggerman, M., van Uum, S., Wiley, K., Panter-Brick, C., 2016. Can stress biomarkers demonstrate the effectiveness of a humanitarian intervention? An evaluation with Syrian refugee youth. In: 41st Annual Meeting of the Human Biology Association. Atlanta, Georgia.

Save The Children, 2017. Invisible Wounds. http://www.savethechildren.org/ (Accessed 10.07.17).

Shonkoff, J.P., Garner, A.S., Siegel, B.S., Dobbins, M.I., Earls, M.F., McGuinn, L., Pascoe, J., Wood, D., 2012. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 129, e232–e246.

Skoluda, N., Dettenborn, L., Stalder, T., Kirschbaum, C., 2012. Elevated hair cortisol concentrations in endurance athletes. Psychoneuroendocrinology 37, 611–617.

Stalder, T., Steudte-Schmiedgen, S., Alexander, N., Klucken, T., Vater, A., Wichmann, S., Kirschbaum, C., Miller, R., 2017. Stress-related and basic determinants of hair cortisol in humans: a meta-analysis. Psychoneuroendocrinology 77, 261–274.

Steudte, S., Kolassa, I.T., Stalder, T., Pfeiffer, A., Kirschbaum, C., Elbert, T., 2011. Increased cortisol concentrations in hair of severely traumatized Ugandan individuals with PTSD. Psychoneuroendocrinology 36, 1193–1200.

Steudte, S., Kirschbaum, C., Gao, W., Alexander, N., Schönfeld, S., Joyer, J., Stalder, T., 2013. Hair cortisol as a biomarker of traumatization in healthy individuals and posttraumatic stress disorder patients. Biol. Psychol. 74, 639–646.

Steudte-Schmiedgen, S., Kirschbaum, C., Alexander, N., Stalder, T., 2016. An integrative model linking traumatization, cortisol dysregulation and posttraumatic stress disorder: insight from recent hair cortisol findings. Neurosci. Biobehav. Rev. 69, 124–135.

Thomson, S., Koren, G., Fraser, L.A., Rieder, M., Friedman, T.C., Van Uum, S.H.M., 2010. Hair analysis provides a historical record of cortisol levels in Cushing's syndrome. Exp. Clin. Endocrinol. Diabetes 118, 133–138.

Tirabassi, G., Boscaro, M., Arnaldi, G., 2014. Harmful effects of functional hypercortisolism: a working hypothesis. Endocrine 46, 370–386.

Tol, W.A., Barbui, C., Galappatti, A., Silove, D., Betancourt, T.S., Souza, R., Golaz, A., van Ommeren, M., 2011a. Mental health and psychosocial support in humanitarian settings: linking practice and research. Lancet 378, 1581–1591.

Tol, W., Patel, V., Tomlinson, M., Baingana, F., Galappatti, A., Panter-Brick, C., Silove, D., Sondorp, E., Wessells, M., van Ommeren, M., 2011b. Research priorities for mental health and psychosocial support in humanitarian settings. PLoS Med. 8 (9), e1001096.

Tol, W.A., Song, S., Jordans, M.J.D., 2013. Annual Research Review: Resilience in children and adolescents living in areas of armed conflict: a systematic review of findings in low- and middle-income countries. J. Child Psychol. Psychiatry 54 (4), 445–460.

UNHCR, 2017. Syrian Regional Refugee Response in Jordan. https://data.unhcr.org/syrianrefugees/country.php?id=107 (Accessed 20.07.17).

Ungar, M., Liebenberg, L., 2011. Assessing resilience across cultures using mixed methods: construction of the child and youth resilience measure. J. Mix Methods Res. 5, 126–149.

Van Ryzin, M.J., Chatham, M., Kryzer, E., Kertes, D.A., Gunnar, M.R., 2009. Identifying atypical cortisol patterns in young children: the benefits of group-based trajectory modeling. Psychoneuroendocrinology 34, 50–61.

Van Uum, S.H.M., Sauve, B., Fraser, L.A., Morley-Forster, P., Paul, T.L., Koren, G., 2008. Elevated content of cortisol in hair of patients with severe chronic pain: a novel biomarker for stress. Stress 11, 483–488.

Veronese, G., Pepe, A., 2013. Psychometric properties of IES-R: short Arabic version in contexts of military violence. Res. Soc. Work Pract. 23, 710–718.

White, L.O., Ising, M., Klitzing, K., Sierau, S., Michel, A., Klein, A.M., Andreas, A., Keil, J., Quintero, L., Müller-Myhsok, B., Uhr, M., 2017. Reduced hair cortisol after maltreatment mediates externalizing symptoms in middle childhood and adolescence. J. Child Psychol. Psychiatry 58 (9), 998–1007.

Wosu, A.C., Valdimarsdóttir, U., Shields, A.E., Williams, D.R., Williams, M.A., 2013. Correlates of cortisol in human hair: implications for epidemiologic studies on health effects of chronic stress. Ann. Epidemiol. 23, 797–811.

Yehuda, R., Goller, J.A., Bierer, L.M., Mikhno, A., Prathett, L.C., Burton, C.L., Makotkine, I., Devanand, D.P., Pradhaban, G., Harvey, P.D., Mann, J.J., 2010. Hydrocortisone responsiveness in Gulf War veterans with PTSD Effects on ACTH, declarative memory hippocampal [(18)F] FDG uptake on PET. Psychiatry Res. 184, 117–127.

Ziadni, M., Hammoudeh, W., Rmeileh, N.M.A., Hogan, D., Shannon, H., Giacaman, R., 2011. Sources of human insecurity in post-war situations The case of Gaza. J. Hum. Secur. 7, 23–36.