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Special Issue Article

Resilience in Development: Pathways to Multisystem Integration

Risk and resilience in Syrian refugee children: A multisystem analysis

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Abstract

Refugee children are often exposed to substantial trauma, placing them at increased risk for mental illness. However, this risk can be mitigated by a capacity for resilience, conferred from multiple ecological systems (e.g., family, community), including at an individual biological level. We examined the ability of hair cortisol concentrations and polygenic scores for mental health to predict risk and resilience in a sample of Syrian refugee children (n = 1359). Children were categorized as either at-risk or resilient depending on clinical thresholds for posttraumatic stress disorder, depression, and externalizing behavior problems. Logistic regression was used to examine main and interacting effects while controlling for covariates. Elevated hair cortisol concentrations were significantly associated with reduced resilience (odds ratio (OR)=0.58, 95%CI [0.40, 0.83]) while controlling for levels of war exposure. Polygenic scores for depression, self-harm, and neuroticism were not found to have any significant main effects. However, a significant interaction emerged between hair cortisol and polygenic scores for depression (OR=0.04, 95%CI [0.003 0.47]), suggesting that children predisposed to depression were more at risk for mental health problems when hair cortisol concentrations were high. Our results suggest that biomarkers (separately and in combination) might support early identification of refugee children at risk for mental health problems.

Keywords: resilience; mental health; refugee children; hair cortisol; polygenic scores

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Introduction

Exposure to war and forced displacement are significant traumata that can severely disrupt the development of refugee children (Maragel & Manachi, 2018; Pieloch et al., 2016). However, not all children will respond equivalently to such atypical stressors due to interindividual differences in each child's resilience and the resilience of the systems in which they are embedded (e.g., family, societal, political, etc.) (Maul et al., 2020). Although multisystemic in nature, the most proximal influences on resilience are those at the biological level (i.e., the genetic and physiological make-up of individual children), but few studies have explored putative biological markers of resilience in refugee populations or children (Stein et al., 2019; Tol et al., 2013). Here, we examine the main and interacting effects of hair cortisol and psychopathology-related polygenic scores in predicting risk and resilience in a large sample of Syrian refugee children.

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Multisystemic resilience

Resilience has been defined as the "the capacity of a dynamic system to adapt successfully to disturbances that threaten system function, viability, or development" (Masten, 2014). From a developmental psychology perspective, humans are the dynamic systems of interest, and resilience is gauged from the patterns of behavior and adaptation emerging in the aftermath of stress (Masten, 2021). Much historical developmental psychology research has examined how children exposed to harmful environments (e.g., poverty, deprivation, abuse) manage to adapt toward healthy, functional adulthood, locating resilience within specific behaviors or stable traits (Popham et al., 2021). Humans, however, are comprised of subordinate systems (e.g., immune, neurological, endocrine, microbial), and are embedded in supraordinate systems (Ungar, 2021b) such as those described in Bronfenbrenner's ecological systems theory (Bronfenbrenner, 1979). Each of these systems undergo constant change and must individually adapt to stressful perturbations, but by virtue of their nested hierarchy, systems dynamically interact and influence each other creating complex patterns of interplay. Consequently, contemporary research acknowledges resilience as a multifaceted process, occurring over time, rather than a single stable factor or trait (Popham et al., 2021).

Interest in resilience research continues to gather momentum in a world currently hallmarked by rapid changes and growing uncertainties (Maul et al., 2020; Ungar, 2021a). Of particular concern are the rising frequency of climate disasters and armed conflict (Masten, 2021), generating a substantial global refugee population, an alarming proportion of which are children (Murray, 2019). The Syrian civil war, for example, has been waged over the past 12 years, forcing over five million Syrian residents, of which approximately 50% are below the age of 18 (Maragel & Manachi, 2018), to flee to neighboring countries. As an interim measure, many refugees are housed within informal tented settlements, but these can be variably beset by issues of overcrowding, limited food security, poor hygiene, and reduced access to education and jobs (Kazour et al., 2017; Murray, 2019). Poor living conditions, war exposure, and forced displacement constitute multiple severe traumas which together demand substantial multisystemic resilience to overcome, driving the need for more comprehensive, transdisciplinary research to mitigate the plight of refugees (Feder et al., 2019).

Childhood resilience

Elucidating resilience in children is of particular importance, given that children are at greater risk for harmful outcomes following exposure to adversity (Murray, 2019; Sirin & Aber, 2018). Childhood represents a critical phase of development, in which many biological and cognitive systems are under development and calibration (Feder et al., 2019; Murray, 2019). Unfortunately, refugee children are often robbed of the experiences and opportunities considered fundamental for positive development. Refugee children typically experience family loss and/or separation (Carlson et al., 2012), and become disconnected from their primary cultures and communities (Cook et al., 2003). Many lack regular access to proper nutrition, sanitation, safe accommodation, or education (Meiqari et al., 2018; Murray, 2019). Amongst those fortunate enough to receive schooling, there may still be challenges with language and acculturation (Pieloch et al., 2016). At further extremes, refugee children may be subjected to rape and sexual violence (especially females), or forced marriage (Hodes et al., 2008; Murray, 2019). All considered, refugee children are exposed to *complex* trauma, that is, multiple traumatic events for an extended period of time (Cook et al., 2003).

As a result of complex trauma, children are likely to experience mental health disorders, physical disorders, and revictimization (Pieloch et al., 2016). Recent estimates indicate that 23–57% of Syrian refugee children meet the clinical diagnosis threshold when scoring posttraumatic stress disorder (PTSD), depression, and/or anxiety symptoms (McEwen et al., 2023; Popham et al., 2022; Sirin & Rogers-Sirin, 2015). However, not all refugee children will succumb to mental illness, with many still retaining a reasonable likelihood of adaptively overcoming their childhood adversities (Murray, 2019). The chances will depend on the resilience of the child, and the resilience of the systems in which the child is ultimately situated at any given time. Since resilience is an ongoing process, even children suffering significant mental health problems may still develop resilience as pertinent systems change (Feder et al., 2019). Identifying the promotive and protective factors manifesting resilience under such severe conditions may inform future strategies for assisting refugee children.

Resilience at the biological level

Although a substantial number of studies have explored psychosocial factors promoting resilience in refugee children (Feder et al., 2019; Pieloch et al., 2016), less is known about biological factors (Maul et al., 2020; Tol et al., 2013). Studies in twins note that resilience is heritable (although to what extent remains unclear), suggesting that biological factors play an appreciable role (Amstadter et al., 2014; Maul et al., 2020). A number of candidate gene studies have highlighted genetic and epigenetic variation in single genes that might have bearing on resilience by virtue of their effects on cognitive (e.g. *SLC6A4*), immunological (e.g. *FKBP5*), or stress-response systems (e.g. *CRHR1*) but trust in candidate gene findings has diminished since the advent of (epi)genome-wide association studies (Duncan et al., 2019; Maul et al., 2020). However, to our knowledge only one genome-wide association study directly examining resilience has been performed to date, which was not sufficiently powered to develop a meaningful polygenic score (a weighted sum of additive genetic influences) capable of predicting resilience (Maul et al., 2020; Stein et al., 2019). Nevertheless, due to biological pleiotropy (Zheutlin et al., 2019), genetic variants associated with relevant phenotypes such as neuroticism, depression, and worry are likely to share association with resilience, depending on how the construct is operationalized (Maul et al., 2020). Polygenic scores for linked phenotypes might thus have utility for predicting resilient outcomes, especially when combined with other biomarkers, but such potential remains largely unexplored (Ahrens et al., 2022).

As a well-established risk factor for mental illnesses, stress-related hormone regulation, particularly cortisol, is likely an informative biological marker of resilience (Masten, 2014; Maul et al., 2020). Cortisol levels tend to appreciably correlate with stress and trauma exposure, although the direction of correlation depends on numerous considerations such as age of the individual, timing of cortisol sampling (morning vs afternoon), sampled tissue, and chronicity of adversity. For example, a study of hair cortisol in girls variably exposed to the 2008 Wenchuan earthquake in China revealed elevated cortisol levels in those with greater exposure (Luo et al., 2012), and hair cortisol was also positively correlated with war exposure in a cohort of Syrian refugee children and adolescents (Smeeth et al., 2023). Similarly, children exposed to recent trauma were discovered to have elevated afternoon salivary cortisol levels, while children with both acute and chronic trauma exposure had lower morning salivary cortisol in addition to higher levels in the afternoon (Bevans et al., 2008). Children exposed to moderate levels of adversity are known to have more robust cortisol responses compared to both highly exposed and unexposed children (Gustafsson et al., 2010), suggesting that cortisol regulation can be indicative of a steeling effect. While cortisol levels have been investigated in numerous psychosocial contexts, results continue to paint a complex picture, and more studies are needed that specifically consider cortisol regulation in children and adolescents demonstrating resilience in the face of adversity (Feder et al., 2019).

Following recent exploration of different psychosocial systems and levels influencing resilience in Syrian refugee children (Popham et al., 2022), we set out to further explore resilience in the same sample by examining factors at the biological level. We operationalized resilience as being below clinically relevant thresholds for PTSD, externalizing and depression symptoms. At-risk children were those meeting the criteria for at least one of the three psychopathologies. We then tested for associations with hair cortisol concentration and a range of polygenic scores for phenotypes linked to mental health which we hypothesize would be associated with reduced resilience. In addition to being a robust indicator of long-term cortisol secretion, hair cortisol might also reflect changes in cortisol secretion over recent months (depending on

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the length of hair sample tested), making hair cortisol a potential measure of both acute stress and longer-term patterns of stress response (Ahrens et al., 2022). Consequently, we hypothesized a strong main effect association between hair cortisol and risk/resilience categorization, even after controlling for appropriate covariates. Because direct associations between resilience and polygenic scores are likely to be of small effect (Choi et al., 2020), and because resilience emerges in response to environmental stressors, we also tested for an interaction between polygenic scores and hair cortisol, hypothesizing that interaction effects would be larger.

Methods

Study participants

Participants were drawn from the biological pathways of risk and resilience in Syrian refugee children (BIOPATH) study (McEwen et al., 2022). Briefly, the BIOPATH study aimed to explore the psychosocial and biological factors underpinning multisystemic resilience and mental health problems in a large cohort of Syrian refugee children. Following ethical review and approval from the Institutional Review Board of the University of Balamand/Saint George Hospital University Medical Center, Lebanon (ref: IRB/O/024-16/1815), the Lebanese National Consultative Committee on Ethics, and the Ministry of Health, purposive cluster sampling was used to recruit refugee families housed in informal tented settlements in the Beqaa region of Lebanon between October 2017 and January 2018. Small-to-medium settlements were selected across seven municipalities, housing refugees classed as the most to third-most vulnerable according to the UNHCR Vulnerability Framework. The informal tented settlements comprised unplanned groups of up to 153 temporary housing structures and families tended to live in large households with a median of 7 individuals per household (IQR: 2–24). Water trucking was the predominate source of clean water in many of these settlements, and while larger settlements contained limited amenities such as a mosque or school, many did not. In each settlement the community leader (chawich) was approached for permission to conduct the study and all eligible families within the settlement were invited to participate. Child–caregiver dyads were eligible to participate if they had left Syria due to the civil war within the previous 4 years, the child was aged 8–16 years at enrollment, and a primary caregiver was available for interview. Of the 2282 families approached, 1600 (70.1%) were both eligible and willing to participate. Due to uncertainty about birth dates, some children outside the intended age range were recruited, and were retained within the sample unless there were concerns about comprehension.

Consenting child–caregiver dyads were interviewed by trained research staff, who administered a range of psychological and other instruments. Research staff were recruited from Lebanon, were required to be bilingual (Arabic and English), and to have recently completed a relevant undergraduate degree. Interview data and biological samples were checked daily by an experienced trial coordinator in Lebanon and regularly by the UK-based team to identify potential errors or problems. Children and caregivers were interviewed simultaneously, but by separate interviewers, in different rooms where possible. When only one room was available, the child and caregiver sat at opposite sides of the room, facing away from each other, and were interviewed in a low voice to maximize privacy. Children assented to providing hair and saliva samples for hair hormone and genetic analyses. The present study includes the subset of children with high quality biological samples and relevant interview data (1359 out of 1594 total participants; filtering steps described in later sections). There was little difference in characteristics between the original cohort and the sample utilized here (Table S1).

Instruments

All instrumentation in the BIOPATH study was translated into Arabic, following the protocol outlined by McEwen et al. (2021), and piloted in the same target population to ensure good psychometric performance. Modifications were made where necessary to improve comprehensibility and performance, and visual aids were often employed to assist children with the Likert scale response format.

Demographic data

Children were asked a series of questions designed to capture key demographic data about themselves and their families. Information was obtained on gender, age, nationality, and general physical health (e.g., recent injuries/illnesses, smoking behavior). Pubertal development was assessed using a shortened version of the Puberty Development Scale (Carskadon & Acebo, 1993; Petersen et al., 1988). As important covariates for hair hormone analyses, children were also asked about the frequency of hair washing and hair alterations (chemical straightening, dyes, etc.). Interviews with caregivers corroborated the information supplied by children. Caregivers also indicated the approximate amount of time that had passed since fleeing Syria.

Mental health outcomes

The Center for Epidemiological Studies Depression Scale for Children (CES-DC) is a widely used self-report questionnaire assessing the frequency of symptoms of depression in children and adolescents (Faulstich et al., 1986). The instrument comprises 20 items, scored on a scale from 0 to 3, with higher scores indicating more frequent symptoms. Good reliability and validity have been demonstrated in numerous previous studies, and the instrument has performed well in diverse settings including Rwanda (Betancourt et al., 2012) and Dubai (Ghubash et al., 2000). Following initial pilot testing for the BIOPATH study, the instrument was reduced to 10 items (each loading strongly onto a single factor) that were more understandable by Syrian refugee children. Internal consistency reliability for the remaining 10 items was high (Cronbach's $\alpha = .88$).

The Child PTSD Symptom Scale and Trauma Symptoms Checklist (CPSS) is a 17-item self-report instrument assessing the severity of DSM-IV PTSD symptoms, designed for use in children aged 8–18 (Foa et al., 2001). Item responses are captured on a scale from 0 to 3, with higher scores indicating more frequent symptoms. In previous studies, the instrument has attained good internal consistency and test–retest reliability (>.70). The CPSS shares a .80 correlation with the Child Posttraumatic Stress Reaction Index (Pynoos et al., 1987), suggesting strong convergent validity. In the present study, the CPSS demonstrated high internal consistency reliability (Cronbach's $\alpha = .91$).

As a measure of externalizing behavior problems, the externalizing subscale of the parent-reported Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) was used, supplemented by additional items assessing oppositional defiant and conduct disorders (McEwen et al., 2022). The SDQ is a 25-item instrument designed to capture psychological attributes of children aged between 3 and 16 years. The instrument can be subscaled in several

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different ways, including a 10-item externalizing subscale comprising items on conduct and hyperactivity/inattention problems. Items were parent-rated on a three-point scale from 0 to 2, with higher scores indicating more externalizing behavior. An additional 12 items aligning to the DSM-5 criteria for conduct disorder and oppositional defiant disorder were also scored along the same scale. Together, the 22 items attained an internal consistency reliability of $\alpha = .80$.

Clinical cut-offs were applied for each mental health scale (12 out of 51 on the CPSS, 10 out of 30 on the abridged CES-DC and 12 out of 44 on the combined externalizing scale total) to define resilience as described previously (Popham et al., 2022). Cut-offs were derived from validation against consensus diagnosis based on structured clinical interviews using the MINI-KID (Sheehan et al., 2010) and expert clinical judgment in a representative subsample ($n = 119$) of the study (McEwen et al., 2021). Resilience was based on a categorical composite of these cut-offs. If participants scored below all three cut-offs, they were considered resilient, but if participants scored above the cut-off for any of the three measures, they were classed as at risk of poor mental health.

Exposure to war

The War Events Questionnaire (WEQ) was designed by the Institute for Development, Research, Advocacy and Applied Care to measure the degree of civilian exposure to war events, specifically for use in Lebanon. The instrument comprises 25 items which assess various experiences of explicit war events such as violence, injury, or kidnapping and was administered to both the child and caregiver. Because self-report may be less reliable in younger children (Oh et al., 2018), child and caregiver responses were combined such that if either one reported that the child experienced an event, the event was considered to have occurred. The WEQ has been used amongst Syrian refugee children previously, where it performed adequately. In our sample, internal consistency reliability for the instrument was high (Cronbach's $\alpha = .88$).

Hair hormones

Hair cortisol concentration was measured as described previously (Smeeth et al., 2023). Hair sections of at least 3 mm in diameter were cut from the posterior vertex of the child's head using clean scissors, packaged in aluminim foil with the scalp end labeled and stored in a cool place before shipping for analysis. Hair samples were taken from 1584 children. Month of collection was noted to account for potential seasonal effects.

Cortisol concentration from hair segments (0–2 cm long) were assayed according to an established ELISA-based protocol (Etwel et al., 2014). Hair sections were weighed, washed with isopropanol, and minced. Cortisol was extracted with methanol overnight at ambient temperature with shaking and evaporated under a stream of nitrogen gas at 60° C until dry. Resulting residues were reconstituted in phosphate-buffered saline before undergoing analysis in duplicate using a modified, commercially available immunoassay (11-CORHU-E01-SLV; ALPCO Diagnostics, USA). Samples exceeding the ELISA's reported detection range were diluted and reanalyzed. Samples below the immunoassay detection limit (1 ng/mL) were not excluded from main analyses due to their bias toward younger females ($n = 227$). The inter-assay coefficients of variation across plates were 6.5–9.8%. Hair cortisol concentration was normalized to sample weight and expressed as ng/g. For all analyses, hair cortisol concentrations were logged (base-10) to ensure a normal distribution. Ten samples were excluded due to outlying values of more than three standard deviations above the mean of the logged hair cortisol, resulting in a final sample of 1574.

Genotypes, imputation, and polygenic scores

Saliva samples were collected using Isohelix GeneFix collection kits. Genomic DNA was extracted and genotyped on the Illumina Infinium Global Screening Array, which types 650,181 genome-wide single nucleotide polymorphisms. Following standard quality control procedures using PLINK version 1.90 (Chang et al., 2015; Purcell et al., 2007), 28 samples were removed due to discrepancies between pedigree and genotyped sex, 68 samples were removed for an individual genotype missing rate > 2%, and a further six samples were removed for outlying heterozygosity rates ($F > 0.2$). Variants with a missing rate > 3%, a minor allele frequency less than 1%, and/or a Hardy–Weinberg equilibrium p-value $< 1 \times 10^{-6}$ were excluded, leaving 420,463 markers.

Imputation of additional genetic variants was performed using the 1000 Genomes Phase 3, Version 5 reference panel and polygenic scores were calculated by means of the Michigan Imputation Server's Genotype Imputation and Polygenic Scores service (Beta version 1.6.10; https://imputationserver.sph.umich.edu). We selected seven psychopathology-related polygenic scores recently found to maintain an average of 72.2% predictive ability in individuals of Middle Eastern ancestry compared to those of European ancestry (Privé et al., 2022). Where possible the polygenic score derived using penalized regression was favored as this exhibited higher predictive ability than the counterpart created using LDpred2. In some cases the LDpred2 version was the only available polygenic score for that phenotype. All seven scores had 100% coverage in our study sample post-imputation (Table 1).

We selected two further polygenic scores for sitting and standing height derived from the same study (Privé et al., 2022) and tested their predictive ability for height within our cohort. Despite the polygenic score being based on an adult European population, there was a significant positive relationship between polygenic scores for sitting and standing height with the respective measurements in the children when controlling for age, gender, and 10 genetic principal components ($B = 0.60$, t (740) = 7.30, $p = 7 \times 10^{-13}$; $B = 1.06$, t (740) = 5.84, $p = 8 \times 10^{-9}$).

Data analysis

Analyses were performed on the subset of children with complete mental health data, valid hair cortisol concentrations, and good quality genetic data according to the filtering described previously ($n = 1359$). The association between predictor variables and the resilience binary outcome was investigated using logistic regression analysis in R (Version 4.2.2; R Core Team, 2013) using the glm function. All analyses controlled for age and gender, while additional covariates were selected based on their reported confounders within the literature. Analyses which utilized hair cortisol also controlled for analysis batch, pubertal stage, hair washing frequency, hair alterations, smoking, and month of collection. Analyses which utilized polygenic scores also controlled for 10 genetic principal components. Results for all included terms are reported excluding batches and principal components due to the high number of terms. Multiple testing was controlled for by applying the false discovery rate (FDR) correction and applying a threshold of 0.1. Moderation effects were investigated by including interaction terms. Significant interactions were interpreted by plotting the marginal effects of log-cortisol and polygenic scores on resilience using the ggeffects R package (Version 1.1.4; Lüdecke, 2018).

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Table 1. Description of polygenic scores

PGS Catalogue identifier	Development method	Reported trait	Number of variants	Coverage in target study
PGS001829	Penalized linear regression	Depression	7534	100%
PGS001898	Penalized linear regression	Ever depressed for a whole week	5777	100%
PGS001899	Penalized linear regression	Recent feelings of depression	2434	100%
PGS001920	Penalized linear regression	Recent feelings of foreboding	2894	100%
PGS001996	Penalized linear regression	Neuroticism score	54715	100%
PGS002113	LDPred2	Depression possibly related to stressful or traumatic event	545334	100%
PGS002222	LDPred2	Ever contemplated self-harm/Recent thoughts of suicide or self-harm	761279	100%
PGS001929	Penalized linear regression	Standing height	156514	100%
PGS002005	Penalized linear regression	Sitting height	118423	100%

PGS Catalogue: https://www.pgscatalog.org.

As a follow-up, the main analyses were repeated using a resilience score based solely on depression and PTSD symptoms to better understand the differences between resilience to all mental health outcomes and resilience to just internalizing disorders. In addition, they were performed only on a subset of the oldest children as previous research suggests that polygenic scores for mental health outcomes derived from adult populations are not strongly predictive in children but show improved predictive ability in adolescents (Khera et al., 2019). Therefore we filtered children according to their pubertal development stage and retained only those in late-post puberty ($n = 224$).

As a sensitivity analysis the same set of analyses were performed excluding genetic outliers (any individual with a principal component value more than four standard deviations from the mean, repeated iteratively until no outliers remained) and genetically related individuals (pi hat > 0.2) to ensure this was not driving associations with polygenic scores ($n = 859$). As an additional sensitivity analysis, they were repeated on matched groups of resilient and at-risk children as described previously in this sample (Popham et al., 2022). Matching was performed using nearest neighbor matching according to Mahalanobis distance in the MatchIt R package (Version 4.5.0; Ho et al., 2011). The groups ($n = 249$ per group) were matched according to their specific pattern of responses across all the individual war exposure items, in addition to child age, gender, and time since leaving Syria, such that each group had identical gender distributions, almost identical mean age and time since leaving Syria, and an almost identical number of children who experienced each war event (standardized mean difference between groups < 0.1 for most items and < 0.2 for all items).

Results

Sample characteristics

After excluding individuals with missing interview data, poor quality genotyping data, and outlying hair cortisol concentrations, we had a sample of 1359 individuals (Table 2). Participants were aged 6–18 years old (mean age = 11.3, SD = 2.4) and evenly split between males and females (47.2% male). As reported previously, participants had experienced significant exposure to war as well as substantial hardship in their current living situation (McEwen et al., 2022). Forty-seven percent of children had left Syria within the past 3 years. The majority of children reported having experienced at least one war-related event (97.2%) and on average children reported 9.6 war-related events (SD = 5.5). Many families were also experiencing inadequate living standards, with 35.8% of families reporting insufficient food and 27.0% of families reporting inadequate heating.

When applying the mental health scale cut-offs determined through clinical interview, 527 (38.8%) were deemed to have significant symptoms of depression, 756 (55.6%) were deemed to have significant symptoms of PTSD, and 598 (44.0%) were deemed to have significant externalizing symptoms. Comorbidity was common with 45% of individuals having significant symptoms of two or more disorders and 13% having significant symptoms of all three disorders. When taking a multidimensional approach to determining resilience, 262 (19.3%) were defined as resilient, with the remainder exhibiting significant symptoms above the cut-off of at least one mental health problem.

Main effects on resilience

We firstly aimed to confirm that war exposure was negatively impacting resilience. A logistic regression was performed to ascertain the effects of war exposure on resilience classification while controlling for age and gender. We found that those reporting a higher number of war-related events had a decreased likelihood of being resilient (odds ratio (OR) = 0.92, 95%CI [0.90, 0.95]; Table S2). Similar results were observed when considering resilience to only internalizing disorders (OR = 0.93, 95%CI [0.91, 0.95]; Table S2).

While the predominate form of trauma experienced by individuals in this cohort occurred during the war, they also experience a wide range of current stressors and adversities in their daily lives. This can be reflected in hair cortisol which acts as an average measure of HPA axis activity over the recent past. We therefore investigated whether hair cortisol, as a biomarker of cumulative stressors, was associated with resilience. We found that those with higher hair cortisol had a decreased likelihood of being resilient (OR = 0.58, 95%CI [0.40, 0.83]; Table 3). Research within this cohort has already shown that war exposure was associated with later elevated hair cortisol, therefore we also controlled for war exposure to ensure that this finding did not simply mimic that found between war exposure and resilience above. We observed a similar relationship between hair cortisol and resilience when

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Table 2. Sample description

N	1359
Male, N(%)	642 (47.24)
Age, mean (SD)	11.3 (2.39)
Pubertal stage N (%)[a]	
Pre-mid puberty	1134 (83.44)
Mid-post puberty	224 (16.48)
Nationality, N(%)	
Syrian	1339 (98.53)
Lebanese	9 (0.66)
Palestinian	9 (0.66)
Other	2 (0.001)
Time since leaving Syria, N (%)[b]	
0–12 months ago	252 (18.54)
12–24 months ago	199 (14.64)
24–36 months ago	193 (14.20)
36–48 months ago	488 (35.91)
>48 months ago	221 (16.26)
Reported smoker, N (%)	16 (1.18)
Recent illness, N (%)	655 (48.20)
Endocrinological medication or illness, N (%)	11 (0.81)
Hair washing frequency, N(%)	
Once per week	93 (6.84)
2–4x per week	830 (61.07)
Daily or 5-6x per week	436 (32.08)
Hair modification N (%)	375 (27.59)
Hair color, N (%)	
Black	899 (66.15)
Brown	443 (32.60)
Other	17 (1.25)
War exposure, median (IQR)	9 (5–14)
Depression symptoms, median (IQR)	7 (2–13)
Depression, N (%)	527 (38.78)
PTSD symptoms, median (IQR)	14 (6–24.44)
PTSD, N (%)	756 (55.63)
Externalizing symptoms, median (IQR)	11 (7–15)
Externalizing, N (%)	598 (44.00)
Resilient, N (%)	262 (19.28)
Cortisol (ng/g), median (IQR)	76.32 (33.66–182.84)

[a]Missing 1 (0.07%). [b] Missing 6 (0.44%).

controlling for war exposure suggesting that this relationship is at least partly due to additional factors (OR = 0.59, 95%CI [0.41, 0.86]; Table 3). Similar findings were observed for internalizing-specific resilience (Table S3).

While the environment is a significant contributor to resilience, individuals also exhibit interindividual variation in resilience, some of which can be explained by genetic factors. We therefore investigated whether a genetic predisposition to various mental health-related phenotypes was associated with resilience within this cohort. Those with high polygenic scores for recent feelings of foreboding (PGS001920) had a lower likelihood of being resilient although this was only statistically significant when additionally controlling for war exposure (OR = 0.01, 95%CI [0.0001, 0.62]; Table 4) and this did not survive controlling for multiple testing. Similar observations were found when analyses were repeated with genetic outliers and related individuals excluded or when using the subset of matched resilient and at-risk individuals (Table S4).

Those with high polygenic scores for ever being depressed for a whole week (PGS001898) also had a lower likelihood of being resilient although this was only statistically significant when war exposure was not controlled for (OR = 0.13, 95%CI [0.02, 0.86]; Table 4). While a stronger association was observed when using the matched sample (OR = 0.06, 95%CI [0.005, 0.86]), no evidence for an association was observed when excluding genetic outliers and related individuals (Table S4).

In contrast, genetic predisposition to phenotypes including previous feelings of depression (PGS001829), recent feelings of depression (PGS001899), depression related to a stressful or traumatic event (PGS002113), ever contemplating suicide or self-harm (PGS002222), or neuroticism symptom score (PGS001996) had no association with risk/resilience grouping in the primary analyses. These findings were similar in most sensitivity analyses although a genetic predisposition for ever contemplating suicide or self-harm (PGS002222) was associated with a greater likelihood of resilience when genetic outliers and related children were excluded (OR = 15,522, 95%CI [4.40, 54713255]).

When these analyses were repeated only considering resilience to internalizing disorders, the association with the polygenic score for recent feelings of foreboding (PGS001920) or ever being depressed for a whole week (PGS001898) were considerably weakened suggesting this finding may be more specific to externalizing symptoms, rather than resilience as a whole (OR = 0.26, 95%CI [0.01, 9.17]; OR = 0.25, 95%CI [0.05, 1.24]; Table S4). The remaining polygenic scores showed no association with resilience to internalizing symptoms.

Finally, we repeated the same analyses with only the oldest individuals as previous reports have suggested that polygenic scores derived from adult populations have higher predictive ability in adolescents compared to children. Polygenic scores for depression (PGS001829) or recent feelings of depression (PGS001899) were both associated with reduced resilience (OR = 0.01, 95%CI [0.0002, 0.31]; OR = 0.00000001, 95%CI [0, 0.07]; Table S4). In contrast, genetic predisposition to depression related to a stressful or traumatic event (PGS002113), ever being depressed for a whole week (PGS001898), ever contemplating suicide or self-harm (PGS002222), or neuroticism symptoms (PGS001996) was not associated with resilience in this older subset.

Interaction analyses

The previous set of analyses showed that while exposure to adversity or biomarkers thereof are associated with a degradation of resilience, genetic predisposition to poor mental health had little impact. However, there was some indication that when taking war exposure into account the association between the exposure of interest and resilience was altered. Therefore we next investigated the synergistic effects of the predictors on resilience.

We first investigated whether hair cortisol moderates the association between war exposure and resilience. We found no evidence for an interactive effect of war exposure and hair cortisol on resilience (OR = 0.95, 95%CI [0.89 1.01]; Table 5). Similar findings

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Table 3. The relationship between cortisol and resilience

	Model 1 (without war exposure)			Model 2 (with war exposure)		
	OR	95% CI	p	OR	95% CI	p
Log-cortisol	0.58	0.40, 0.83	0.003	0.59	0.41, 0.86	0.006
Gender[a]	1.50	1.08, 2.08	0.016	1.44	1.04, 2.02	0.030
Age	0.97	0.90, 1.05	0.447	1.00	0.92, 1.08	0.949
Smoking status[b]	0.00	0, +Inf	0.473	0.00	0, +Inf	0.970
Hair alterations[c]	0.87	0.62, 1.23	0.439	0.88	0.63, 1.24	0.473
Hair washing frequency[d]						
2–4 times per week	1.34	0.75, 2.39	0.327	1.32	0.74, 2.39	0.349
Daily or 5–6 times per week	0.85	0.46, 1.59	0.621	0.90	0.48, 1.68	0.731
Pubertal stage[e]	0.81	0.48, 1.36	0.423	0.76	0.45, 1.29	0.307
Collection month[f]						
November	1.75	0.65, 4.75	0.121	1.58	0.57, 4.35	0.377
December	1.63	0.47, 5.73	0.855	1.38	0.39, 4.96	0.620
January	0.95	0.26, 3.45	0.443	0.68	0.18, 2.52	0.563
War exposure	–	–	–	0.92	0.90, 0.95	$2x10^{-8}$

Reference levels: [a]Male, [b]No, [c]No, [d]Once per week, [e]Pre-mid puberty, [f]October. Main effects of batches not shown for clarity.

were observed when investigating resilience to just internalizing disorders and limiting analysis to those who were in the later stages of puberty (Table S5).

Next, we investigated whether the polygenic scores for mental health outcomes moderate the association between war exposure and resilience. Again, we found no strong evidence for an interactive effect between war exposure and any polygenic score on resilience (Table S6). Finally we investigated whether the polygenic scores for mental health outcomes moderate the association between hair cortisol and resilience. While there was no evidence for a moderation effect involving most polygenic scores, the interaction between the polygenic score for depression (PGS001829) and hair cortisol was significantly associated with resilience (OR = 0.04, 95%CI [0.003 0.47]; Table 6). Further investigation of this interaction indicated that while those with a lower genetic predisposition for depression had little relationship between hair cortisol and resilience likelihood, those with a higher genetic predisposition had a stronger negative relationship between cortisol and likelihood of resilience (Figure 1).

Discussion

A holistic appreciation of resilience requires an examination of the construct across multiple systems (individual, family, community, etc.), at different levels within each system (Ungar, 2021b). Although psychosocial and environmental influences on resilience are well described, transdisciplinary investigations of biological-level resilience are only beginning to gather momentum (Feder et al., 2019; Masten, 2021). Building on our previous exploration of resilience in Syrian refugee children (Popham et al., 2022), we examined the potential of hair cortisol concentrations and polygenic scores for mental health outcomes to predict resilience to internalizing and externalizing mental health problems.

Regarding main effect analyses, war exposure was significantly associated with decreased resilience. Early experiences of trauma, such as war events, are known to significantly dysregulate childhood physiological development, hampering stress response and cognitive functioning, with downstream impacts on behavior regulation (De Bellis & Zisk, 2014), social competencies, attention, memory, and general academic performance (Dye, 2018). Exposure to complex trauma compounds these issues, leading to greater symptom severity and complexity (Dye, 2018). Such impairment at multiple physiological and cognitive levels will understandably diminish the capacity for resilience in children, particularly refugees, supporting our significant findings.

We also detected a significant association between elevated hair cortisol concentrations and decreased resilience, even when controlling for war exposure. Cortisol concentrations are a well-described proxy often used to gauge physiological stress responses (Steudte-Schmiedgen et al., 2016) and sampling hair allows the assessment of major events over the recent past (Karlén et al., 2011). Elevated cortisol levels have been reliably detected in other stressful contexts such as shift-work (Manenschijn et al., 2011), unemployment (Dettenborn et al., 2010), and chronic pain (Van Uum et al., 2008). Similar to our findings, Ahrens et al. (2022) discovered that elevated hair cortisol distinguished individuals suffering acute mental deterioration versus those more resilient following COVID-19 lockdown. Dajani et al. (2018) noted that cortisol hypersecretion characterized adolescent Syrian refugees who felt more fearful and insecure post-migration. However, to what extent hair cortisol reflects trait components (e.g., an inherited disposition toward elevated cortisol secretion) of stress response versus state influences (e.g. environmental stressors) is not fully apparent (Ahrens et al., 2022). Although evidence suggests hair cortisol is more reflective of strong trait elements (Stalder & Kirschbaum, 2012), concentrations remain reliably correlated to the severity of, and time since, traumatization (Steudte-Schmiedgen et al., 2016). In our study, hair cortisol did not moderate the effects of war exposure on resilience, possibly indicating less of a trait component, or one less detectable in young children. Instead, our results suggest that state influences including both

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Table 4. The relationship between polygenic scores and resilience

	Model 1 (without war exposure)				Model 2 (with war exposure)			
	OR	95% CI	p	FDR-corrected p[b]	OR	95% CI	p	FDR-corrected p
PGS(Depression)	0.89	0.26, 3.01	0.854	0.845	0.94	0.28, 3.22	0.926	0.926
Gender[a]	1.26	0.96, 1.66	0.101		1.22	0.92, 1.62	0.159	
Age	0.91	0.86, 0.97	0.003		0.94	0.88, 1.00	0.041	
War exposure	–	–	–		0.92	0.90, 0.95	1×10^{-8}	
PGS(Ever depressed)	0.13	0.02, 0.86	0.035	0.163	0.15	0.02, 1.03	0.053	0.133
Gender[a]	1.27	0.96, 1.67	0.089		1.24	0.93, 1.64	0.137	
Age	0.92	0.86, 0.97	0.004		0.94	0.89, 1.00	0.048	
War exposure	–	–	–		0.92	0.90, 0.95	1×10^{-8}	
PGS(Recent depression)	0.16	0.00, 15.7	0.436	0.610	0.16	0.00, 16.0	0.434	0.608
Gender[a]	1.26	0.96, 1.66	0.102		1.22	0.92, 1.61	0.161	
Age	0.91	0.86, 0.97	0.003		0.94	0.88, 1.00	0.042	
War exposure	–	–	–		0.92	0.90, 0.95	1×10^{-8}	
PGS(Recent foreboding)	0.02	0.00, 1.10	0.056	0.163	0.01	0.00, 0.62	0.029	0.133
Gender[a]	1.27	0.96, 1.67	0.091		1.24	0.93, 1.63	0.139	
Age	0.91	0.86, 0.97	0.003		0.94	0.88, 1.00	0.042	
War exposure	–	–	–		0.92	0.90, 0.95	6×10^{-9}	
PGS(Neuroticism)	0.89	0.68, 1.16	0.376	0.610	0.88	0.67, 1.16	0.370	0.608
Gender[a]	1.27	0.96, 1.67	0.093		1.23	0.93, 1.63	0.146	
Age	0.91	0.86, 0.97	0.003		0.94	0.88, 1.00	0.040	
War exposure	–	–	–		0.92	0.90, 0.95	1×10^{-8}	
PGS(Depression after trauma)	27.35	0, 6776436	0.602	0.702	49.19	0, 14299905	0.544	0.635
Gender[a]	1.26	0.96, 1.66	0.097		1.23	0.93, 1.62	0.152	
Age	0.91	0.86, 0.97	0.003		0.94	0.88, 1.00	0.043	
War exposure	–	–	–		0.92	0.90, 0.95	1×10^{-8}	
PGS(Thoughts of self-harm)	315.70	0.62, 159824	0.070	0.163	460.60	0.84, 252136	0.057	0.133
Gender[a]	1.27	0.97, 1.68	0.087		1.23	0.93, 1.63	0.146	
Age	0.91	0.86, 0.97	0.002		0.94	0.88, 0.99	0.032	
War exposure	–	–	–		0.92	0.90, 0.95	9×10^{-9}	

Reference levels: [a]Male. [b]FDR-corrected p-values for main effects of each PGS only. Main effects of PCAs not shown for clarity.

earlier and current adversities may reduce childhood resilience. Nevertheless, hair cortisol levels may serve as a convenient measure that collates the effects of genetically predisposed traits with acute and chronic traumas, earmarking hair cortisol as a particularly promising biomarker (Steudte-Schmiedgen et al., 2016).

In contrast, polygenic risk for various mental health-related outcomes was not clearly associated with resilience. Although scores for recent feelings of foreboding (PGS001920) and ever feeling depressed for a whole week (PGS001898) exhibited promising links to resilience, these associations did not hold up under further scrutiny (multiple testing correction and sensitivity analyses). These findings were somewhat unsurprising, given that polygenic scores typically account for a small amount of phenotypic variation, especially for behavioral phenotypes which often have strong environmental components (Smeland & Andreassen, 2021). Moreover, polygenic scores are known to suffer deflation when applied to ethnicities other than those used to train the scoring algorithm (Choi et al., 2020). Scores used in our study (which were mostly trained on European data) were previously acknowledged to deflate by 28% on average when scoring individuals of Middle

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Table 5. The moderating relationship of cortisol and war exposure on resilience

	OR	95% CI	p
Log-cortisol	0.85	0.47, 1.55	0.605
War exposure	1.00	0.90, 1.12	0.970
Log-cortisol × War exposure	0.96	0.90, 1.01	0.135
Gender[a]	1.48	1.06, 2.06	0.023
Age	1.00	0.92, 1.08	0.916
Smoking status[b]	0.00	0.00, +Inf	0.970
Hair alterations[c]	0.88	0.62, 1.24	0.453
Hair washing frequency[d]			
2–4 times per week	1.31	0.73, 2.35	0.371
Daily or 5–6 times per week	0.88	0.47, 1.66	0.703
Pubertal stage[e]	0.76	0.45, 1.29	0.312
Collection month[f]			
November	1.54	0.56, 4.26	0.406
December	1.36	0.38, 4.87	0.642
January	0.68	0.18, 2.53	0.564

Reference levels: [a]Male, [b]No, [c]No, [d]Once per week, [e]Pre-mid puberty, [f]October. Main effects of batches not shown for clarity.

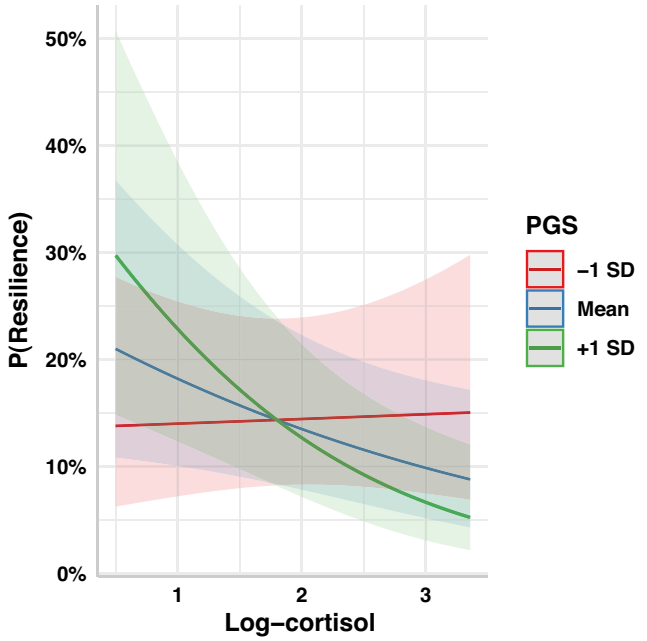

Figure 1. Marginal estimates for the association between hair cortisol and probability of resilience for representative levels of polygenic risk for depression (PGS001829). Individuals one standard deviation above the mean polygenic risk for depression (PGS = 0.07; green line) were most likely to be resilient at low levels of cortisol secretion, but were the least likely to be resilient at high levels of secretion. Children with the mean polygenic risk (PGS = −0.04; blue line) displayed a more gradual decline in resilience probability with increasing cortisol secretion. Meanwhile, children one standard deviation below the mean polygenic risk (PGS = −0.16; red line) displayed a stable probability of resilience regardless of cortisol secretion. Shaded regions indicate 95% confidence intervals.

Eastern ancestry (Privé et al., 2022). Deflation is attributed to multiple issues, including differences in linkage disequilibrium patterns, allele frequencies, effect sizes, and environments.

Score deflation might have been further exacerbated in our study due to the age of participants. Only amongst an older subset of children was there some evidence that polygenic scores for selected phenotypes were associated with reduced resilience. This supports the idea that adult-based polygenic scores are not immediately valid for younger populations (Lange et al., 2022) and that genetic predisposition to poor mental health may not be identical between children and adolescents. Genotype expression likely changes in response to aging, with different genes influencing phenotypes across different age ranges (de Zeeuw et al., 2014). Given that an overwhelming majority of refugees are of non-European ancestry (Murray, 2019), and almost half are below the age of 18, there is even greater impetus for future polygenic score development to be more inclusive of other ancestries and age ranges, especially if polygenic scores are to realize their potential for more personalized medicine and treatment (Smeland & Andreassen, 2021).

Due to the anticipated lack of main effects, we hypothesized that interaction effects between polygenic scores and environmental variables (war exposure, hair cortisol) would be more discernible. However, only one interaction, between hair cortisol and polygenic risk for depression (PGS001829), emerged as significant. Children with a higher genetic predisposition to depression were more likely to be classed as resilient at lower levels of hair cortisol, but the probability of resilience diminished appreciably as cortisol concentration increased. Associations and interactions between hair cortisol and polygenic scores are a recent area of interest in the literature (Ahrens et al., 2022; Bolhuis et al., 2019; Rietschel et al., 2017), driven by the appreciation that hair cortisol captures both heritable and environmentally influenced aspects of stress regulation. However, current results remain underwhelming. Rietschel et al. (2017) found no correlation between hair cortisol and polygenic scores for Neuroticism and Major Depressive Disorder. Similarly, there was no significant moderating effect of hair cortisol on compound sets of polygenic scores related to internalizing, psychotic, neurodevelopmental, or dysfunctional coping disorders in predicting mental health trajectories following COVID-19 lockdown (Ahrens et al., 2022). Bolhuis et al. (2019) did, however, identify a significant interaction between hair cortisol and a polygenic score for schizophrenia in predicting components of pre-adolescent brain structure, although this did not survive correction for multiple testing. Our results are potentially a further indication that high cortisol levels can trigger underlying genetic predispositions to mental illness, but this interaction might capture only a marginal difference in risk or resilience and awaits validation in independent studies.

Over 80% of refugee children are estimated to exhibit psychosocial problems that often stem from disrupted development (Fegert et al., 2018), and these can strain the ability of supraordinate systems to confer supporting resilience. For example, caretakers may struggle to cope with the needs of traumatized children and may respond in ways that unintentionally exacerbate their weakened resilience (e.g., insensitive parenting, verbal threats, physical abuse) (Eruyar et al., 2018; Punamäki et al., 2018). The negative consequences of trauma exposure in childhood can persist well into adulthood, continuing to undermine a capacity for resilience (Dye, 2018). Such long-term and knock-on effects across systems of resilience underpin the current emphasis on transdisciplinary investigations that can widen our understanding of promotive and predictive factors of resilience, especially within children (Masten, 2021). Our study provides empirical evidence

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Table 6. The moderating relationship of cortisol and polygenic scores on resilience

	OR	95% CI	p	FDR-corrected p
PGS(Depression)	349.60	3.11, 39350	0.015	
Hair cortisol	0.62	0.43, 0.88	0.008	
PGS × Hair cortisol	0.04	0.00, 0.47	0.010	0.070
PGS(Ever depressed)	15.34	0.01, 18248	0.450	
Hair cortisol	0.66	0.46, 0.94	0.021	
PGS × Hair cortisol	0.08	0.00, 3.43	0.188	0.182
PGS(Recent depression)	0.00	0, 153630	0.505	
Hair cortisol	0.65	0.38, 1.11	0.114	
PGS × Hair cortisol	10.21	0, 128238	0.630	0.439
PGS(Recent foreboding)	0.00	0, 0.04	0.018	
Hair cortisol	0.75	0.54, 1.06	0.100	
PGS × Hair cortisol	3852.65	0.93, 15949597	0.052	0.553
PGS(Neuroticism)	0.60	0.21, 1.67	0.325	
Hair cortisol	0.63	0.40, 1.00	0.051	
PGS × Hair cortisol	1.26	0.72, 2.18	0.419	0.587
PGS(Depression after trauma)	1467757963	0, +Inf	0.390	
Hair cortisol	0.86	0.49, 1.49	0.587	
PGS × Hair cortisol	0.00	0, 3767498.69	0.444	0.518
PGS(Thoughts of self-harm)	39650407	0, +Inf	0.157	
Hair cortisol	0.80	0.55, 1.15	0.229	
PGS × Hair cortisol	0.00	0, 452.9	0.316	0.630

Main effects of additional covariates not shown for clarity.

that elevated hair cortisol concentrations might be a useful biomarker for identifying refugee children at greater risk for mental health problems. Polygenic scores alone do not appear to be a similarly useful marker in this regard, aligning with their current lack of clinical utility (Smeland & Andreassen, 2021). However, combinations of markers such as hair cortisol and polygenic scores might hold some benefit, but further studies are required.

Limitations

Several limitations to our study should be noted. Firstly, our definition of resilience was based solely on the absence of diagnosable mental health problems (of three limited types), which simplifies a far more nuanced construct, likely limiting our power to detect associations. While we conducted follow-up analyses to disentangle the distinct associations with resilience to externalizing and internalizing problems, we acknowledge that our approach may be biasing results toward the more prevalent mental health problems within our sample. We were also unable to incorporate anxiety and other mental health problems into the resilience profiling, therefore we may be misclassifying children as resilient when in fact they might be experiencing significant mental distress or impairment.

Secondly, although our sample size was adequate for main effect analyses, it was appreciably underpowered to detect interactions, particularly those involving polygenic scores. This is likely exacerbated by the impaired predictive ability of polygenic scores derived from adult European populations in our younger Syrian cohort. The main effects of psychopathology-related polygenic scores were mostly insignificant, despite polygenic scores for height demonstrating a clear predictive ability in our sample. However, height has a large, stable genetic component (Wood et al., 2014), whereas resilience and mental health outcomes are more dynamic constructs with wider sets of environmental influences.

Lastly, due to the cross-sectional design of our analysis, no causal inferences can be made. These are critical if measures of stress responses like hair cortisol concentrations are to be used for prediction or stratification before the onset of mental health symptomology. Importantly, Dajani and colleagues (2018) found that measures of hair cortisol in highly traumatized adolescent Syrian refugees were dysregulated, showing no clear relationship across three time-points (2.8 and 11.3 months after baseline

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measures). The lack of correlation was ascribed to the complex change in cortisol production from hyper- to hyposecretion as stress shifts from acute to chronic – an occurrence typical for refugees. This phenomenon of "cortisol blunting" highlights the importance of longitudinal investigations, capable of delineating cortisol trajectories, that are more informative than single time-point assessments.

Conclusion

In conclusion, our study highlights the potential of biological markers (particularly hair cortisol) to augment the identification of at-risk and resilient refugee children. There remain, however, substantial complexities that need to be unpacked in future research (e.g., cortisol blunting; ethnicity-specific polygenic scores) before biological markers can serve as credible screening tools in refugee contexts. Moreover, the true utility of these markers may lie in discernible interaction effects, both between biological markers, and between biological markers and more distal systems of resilience. Early and objective identification of children's degree of risk could ultimately improve the timing and efficacy of psychosocial interventions aimed at alleviating mental health burdens and strengthening multisystemic resilience.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579423000433.

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